# Diabetic Optic Neuropathy and Its Risk Factors in Chinese Patients With Diabetic Retinopathy

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**Purpose.** To investigate diabetic optic neuropathy (DON) prevalence and risk factors in Chinese diabetic retinopathy (DR) patients.

**Methods.** This retrospective study included 1067 eyes (550 patients) that underwent ocular imaging. The diabetes duration, systolic blood pressure (SBP), hemoglobin A1c (HbA1c), and high-density lipoprotein (HDL) were also recorded simultaneously.

**Results.** A total of 410 eyes with DON and 657 eyes without DON were included (38.4% DON prevalence). DON eyes were classified as having diabetic papillopathy (DP), optic disc neovascularization (NVD), anterior ischemic optic neuropathy (AION), or optic atrophy (OA). Proliferative DR eyes had a higher DON prevalence than nonproliferative DR eyes ($P < 0.001$). Diabetes duration, SBP, and HbA1c were higher in DON patients than in non-DON patients (all $P < 0.001$). Additionally, HDL was lower in patients with DON (0.74 ± 0.13 mM) than in those without DON (1.00 ± 0.24 mM, $P < 0.001$). HbA1c levels were greater in AION patients (10.00 ± 1.53% [85.76 ± 16.71 mmol/mol]) than in DP patients (8.78 ± 1.97% [72.45 ± 21.55 mmol/mol], $P = 0.017$); central foveal thickness (CFT) significantly varied among groups ($P < 0.001$). Increased age, diabetes duration, SBP, CFT, and DR severity were risk factors for DON; and increased HbA1c was a risk factor for NVD, AION, and OA (all $P < 0.05$).

**Conclusions.** Our study results strengthen the argument that increased age, diabetes duration, SBP, CFT, DR severity, and HbA1c are all risk factors for DON in patients with DR.

Keywords: diabetic optic neuropathy, diabetic papillopathy, risk factors, fundus fluorescein angiography, optical coherence tomography

The prevalence of diabetes mellitus (DM) is increasing worldwide. Diabetic patients have a variety of systemic and ocular health conditions, with the most common ocular complications being diabetic retinopathy (DR) and diabetic macular edema.[1] However, various forms of diabetic optic neuropathy (DON) can also develop, some of which can threaten vision. The prevalence of DON is often underestimated in clinical practice, especially in China.

Diabetic papillopathy (DP) is a self-limiting, progressive, unilateral, or bilateral form of DON that can affect both type 1 and type 2 diabetics.[1] Patients with DP are generally young and have normal functioning pupils but commonly present with mild blurry or distorted vision, an enlarged blind spot, unilateral or bilateral disc swelling, superficial dilated disc telangiectasia, and disc hyperfluorescence with late fluorescein angiography (FFA) leakage.[2] Fortunately, DP tends to be mild and is usually associated with a good visual prognosis, but some patients develop a permanent visual impairment.[1] Risk factors for developing DP include a pronounced increase in hemoglobin A1c (HbA1c) levels and a small cup-to-disc ratio.[3] Appen et al.[4] hypothesized that DP patients sustain a local optic disc vasculopathy, presumably associated with diabetes. This vasculopathy causes transient fluid leakage and results in disc edema. The physical presence of edema can disrupt axoplasmic flow, and in the presence of prolonged hyperglycemia and anoxia, can cause optic nerve toxicity from improper glucose utilization.[5] Vitreopapillary traction can also develop and cause disc edema in eyes with DP.[6]

Optic neuropathies other than DP can develop in diabetic patients including optic disc neovascularization (NVD), nonarteritic anterior ischemic optic neuropathy (AION), and optic atrophy (OA), which were also regarded as DON in China.[7] It has been shown that DM significantly increases the risk of developing AION.[8] Reddy et al.[9] reported an AION prevalence of 30.1% in eyes with DR and a prevalence of 13.1% in eyes with vision-threatening DR. Both DP and AION are ischemic optic neuropathies. While eyes with DP are asymptomatic, eyes with AION have an acute optic disc infarction.[2] However, there is some overlap between AION and DP; for instance, 36% of DP cases eventually progress to AION.[10] Therefore, it is important to identify eyes with DP so that they can be closely monitored for more serious conditions threatening vision. The current study investigated the prevalence of DON (including DP, AION, NVD, and OA) in Chinese DR patients. Clinical characteristics of DR patients with and without DON were also examined and compared, to identify risk factors for developing DON.

## Materials and Methods

This retrospective, cross-sectional, hospital-based study was reviewed and approved by the Institutional Review Board of the First Hospital of China Medical University, Shenyang, China.

This research adhered to the tenets of the Declaration of Helsinki and all patients provided written informed consent for their medical information to be included in our study. Prior to obtaining consent from patients, potential risks associated with systemic (age, sex, diabetes duration, systolic blood pressure [SBP], HbA1c levels, and high density lipoprotein [HDL] levels) and ocular (DR severity and central foveal thickness [CFT]) characteristics were fully discussed.

### Study Subjects

Patients with type 2 diabetes who were diagnosed with DR and referred to the First Hospital of China Medical University for ophthalmologic evaluation between January 2008 and January 2017 were included in this study. All subjects underwent a complete ophthalmic examination, which included fundus photography, FFA, and optical coherence tomography (OCT). Ophthalmic examination results and the following systemic parameters were recorded: diabetes duration, SBP, HbA1c levels, and HDL levels. Patients who had other retinal diseases, poor-quality imaging, or a history of ocular interventions (e.g., laser photocoagulation, vitrectomy, or anti-vascular endothelial growth factor injection in either eye) were excluded from the study. Patients with missing eye data were also excluded. All eyes with DR were classified into the following DON categories: non-DON, DP, NVD, AION, and OA.[7] To be placed in the DP group, patients needed to have a confirmed diabetes diagnosis and isolated unilateral or bilateral optic disc edema with normal intracranial pressure, no substantial optic nerve dysfunction, and no optic disc inflammation, infiltration, or infection.[1]

### Data Collection

Demographic, systemic, and ocular characteristics were obtained from subject medical records and included age, sex, hypertension status, diabetes duration, and ophthalmic history. Based on dilated ophthalmoscopy findings of two ophthalmologists, DR severity was graded using the International Clinical Diabetic Retinopathy Disease Severity Scales[11] and DON was classified using the Zhongshan Ophthalmic Center's study.[7] If there was a discrepancy between disease grading or classification, both ophthalmologists discussed the case with a retinal specialist and came to a consensus. The CFT was manually measured on OCT images by the same two ophthalmologists who graded DR severity and classified DON. The average of the two values was used in the analyses.

### Statistical Analyses

Data are presented as mean ± standard deviation for variables with a normal distribution, and as geometric means (95% confidence intervals [CIs]) for variables not distributed normally. Relationships between DR severity, sex, and DON were examined using the Pearson $\chi^2$ test and a stratified $\chi^2$ test. The stratified $\chi^2$ test was performed using the following equation:

$$P = a/[K \times (K-1)/2 + 1]$$

where $P$ = corrected probability, $a = 0.05$, and $K$ = number of groups. Differences in age, SBP, diabetes duration, CFT, HbA1c levels, and HDL levels were examined among the five DON groups using the 1-way ANOVA test. PDR patients with and without DON were compared using the Pearson $\chi^2$ test and independent-samples $t$-test. Predictors for DON development were examined using multiple logistic regression analyses that were adjusted for age, sex, diabetic duration, SBP, DR severity, CFT, HbA1c levels, and HDL levels. Odds ratios (ORs) and 95% CIs were also calculated. All statistical analyses were performed using SPSS statistical software (version 18.0; SPSS, Inc., Chicago, IL, USA) and statistical significance was defined as $P < 0.05$.

**Table 1.** Effect of Diabetic Retinopathy Severity on Diabetic Optic Neuropathy Incidence

| DON | Nonproliferative DR (Eyes) | Proliferative DR (Eyes) | *P* |
|---|---|---|---|
| Total | 497 | 570 | |
| Non-DON | 466 (93.8%) | 191 (33.5%) | <0.001 |
| DON* | 31 (6.2%) | 379 (66.5%) | |
| DON subtypes | | | |
| DP* | 7 (1.4%) | 25 (4.4%) | <0.001 |
| NVD*† | 2 (0.4%) | 104 (18.2%) | <0.001 |
| AION* | 22 (4.4%) | 232 (40.7%) | <0.001 |
| OA* | 0 (0%) | 18 (3.2%) | <0.001 |

Statistical significance of intergroup differences was determined using the stratified $\chi^2$ test.

* Indicates significantly different from non-DON eyes ($P < 0.001$).

† Indicates significantly different from DP eyes ($P < 0.001$).

## Results

### Study Subjects

A total of 1067 eyes of 550 DR patients (235 males, 315 females) were eligible for this study (Fig. 1). Mean subject age was 55.1 ± 10.4 years (range, 26–84 years), mean diabetes duration was 12.3 ± 6.6 years (range, 0.1–39.0 years), and mean SBP was 128.12 ± 20.40 mm Hg (range, 100.00–193.00 mm Hg). In the 153 patients (27.8%) that underwent laboratory testing, mean HbA1c and HDL levels were 8.42 ± 1.72% (68.58 ± 18.82 mmol/mol) and 0.91 ± 0.24 mmol/L, respectively. Mean logMAR best-corrected visual acuity was 0.483 ± 0.425 (Snellen equivalent: 20/61). A total of 570 eyes (53.4%) had proliferative DR (PDR) and 497 eyes (46.6%) had nonproliferative DR (NPDR, Fig. 1). All eyes underwent OCT examination and mean CFT was 254.69 ± 131.90 μm.

### Diabetic Optic Neuropathy

A total of 410 eyes of 247 subjects had DON (44.9% subject incidence, 38.4% ocular incidence; 163 bilateral cases, 84 unilateral cases). Of the included 1067 eyes, 32 eyes had DP (3.0%), 106 eyes had NVD (9.9%; 104 eyes with retinal neovascularization, 2 eyes with a proliferative fibrous membrane at the disc), 254 eyes had AION (23.8%), and 18 eyes had OA (1.69%). Of the 410 eyes with DON, 31 eyes (7.6%) had NPDR and 379 eyes (92.4%) had PDR ($P < 0.001$, Table 1).

**Effect of Systemic Parameters.** There was significant age difference between subjects with DON (58.0 ± 11.2 years) and without DON (53.3 ± 9.5 years, $P < 0.001$). Moreover, subjects with AION (62.0 ± 9.5 years) were significantly older than subjects without DON (53.3 ± 9.5 years) and with other DON types (DP: 52.5 ± 12.8 years, NVD: 50.9 ± 10.1 years, OA: 53.5 ± 10.8 years; all $P < 0.05$).

The sex distribution between subjects with DON (101 men of 247 subjects [40.9%]) and without DON (157 men of 303 subjects [51.8%]) was not significantly different ($P = 0.075$). However, sex distribution differences among the five study groups was statistically significant ($\chi^2 = 15.673$, $P = 0.003$). More specifically, the AION group (26.8% female) contained more women than the NVD group (7.9% female, $P = 0.001$).

Systolic blood pressure was significantly higher in DON patients (154.12 ± 12.04 mm Hg) than in non-DON patients (128.95 ± 15.35 mm Hg, $F = 147.66$, $P < 0.001$). Additionally,

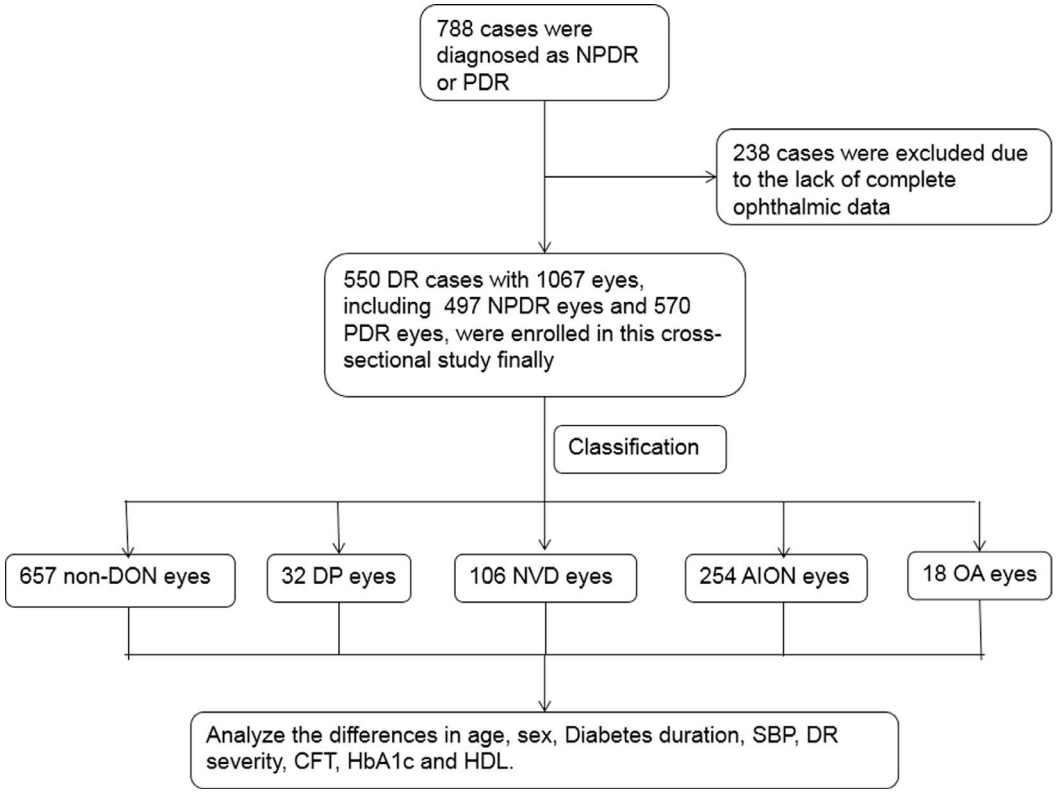


**Figure 1.** Data collection.

SBP was significantly lower in DP subjects (153.12 ± 17.48 mm Hg) than in NVD ones (162.15 ± 17.02 mm Hg, $P < 0.001$), and in AION subjects (148.46 ± 17.90 mm Hg) than in OA subjects (158.72 ± 23.56 mm Hg, $P < 0.05$, Fig. 2A).

Subjects who developed DON had a diabetes duration of 16.9 ± 6.4 years. This was significantly higher than for subjects who had not developed DON (9.4 ± 4.9 years, $P < 0.001$). There were also some disease duration differences among DON subgroups. DP and NVD subjects had a shorter diabetes duration than subjects with AION and OA (Fig. 2B). Furthermore, disease duration progressively increased from the non-DON group to the OA group (lowest to highest order: non-DON, DP, NVD, AION, OA; $F = 128.9$, $P < 0.001$).

Significant differences in HbA1c and HDL levels were also observed among DON groups. The HbA1c levels were significantly higher in subjects with DON (9.82 ± 1.64% [83.84 ± 17.91 mmol/mol]) than without DON (7.77 ± 1.33% [61.42 ± 14.51 mmol/mol]; $F = 35.57$, $P < 0.001$). Additionally, HbA1c levels in the AION group were significantly greater than in the DP group (Fig. 2C). The HDL levels were significantly lower in DON subjects (0.74 ± 0.13 mmol/L) than in non-DON subjects (1.00 ± 0.24 mM, $P < 0.05$). This was also true for all DON subgroups (DP: 0.71 ± 0.08 mmol/L, NVD: 0.71 ± 0.10 mmol/L, AION: 0.75 ± 0.15 mmol/L, OA: 0.70 ± 0.08 mmol/L; $P < 0.05$).

**Effect of Ocular Parameters.** PDR subjects had a significantly higher rate of DON (66.5%) than NPDR ones (6.2%, $P < 0.001$). Additionally, eyes with NVD were more likely to have PDR than eyes with DP ($P < 0.001$, Table 1).

Mean CFT was 205.11 ± 89.57 μm in eyes without DON and 334.16 ± 149.00 μm in eyes with DON ($P < 0.001$). Furthermore, mean CFT was 370.16 ± 133.2 μm in eyes with DP, 412.20 ± 155.47 μm in eyes with NVD, 303.59 ± 135.88 μm in eyes with AION, and 241.83 ± 119.54 μm in eyes with OA. Differences among the five DON groups were statistically significant ($F = 105.7$, $P < 0.001$). More specifically, the DP group had a significantly greater CFT than the AION ($P = 0.002$), OA ($P < 0.001$), and non-DON ($P < 0.001$) groups. Additionally, CFT in AION was greater than that in OA ($P = 0.024$, Fig. 2D).

**Comparison Between PDR With and Without DON.** Compared with PDR patients without DON, those with DON had higher age, diabetes duration, SBP, HbA1c, and CFT. In contrast, HDL was lower in those with PDR and DON than in those with PDR without DON. However, there was no significant difference in terms of sex between the two groups (Table 2).

**Risk Factors for Developing Diabetic Optic Neuropathy.** Multiple logistic regression analysis adjusted for age, sex, diabetes duration, SBP, DR severity, and CFT revealed that increasing age, diabetes duration, and SBP increased the risk for developing DP, NVD, and OA (all $P < 0.05$). Additionally, the risk of developing DP, NVD, and AION increased with

**Table 2.** Comparison Between PDR With and Without DON

| | PDR With DON | | PDR Without DON | | |
|---|---|---|---|---|---|
| **Parameter** | **No.** | **Value** | **No.** | **Value** | ***P*** |
| Sex (male) | 379 | 162 (42.7%) | 191 | 81 (42.4%) | 0.94* |
| Age, y | 379 | 58.19 ± 11.30 | 191 | 54.52 ± 9.33 | <0.001 |
| Duration, y | 379 | 16.98 ± 6.43 | 191 | 11.43 ± 5.25 | <0.001 |
| SBP, mm Hg | 379 | 153.20 ± 18.66 | 191 | 130.81 ± 15.83 | <0.001 |
| HbA1c, % | 92 | 9.84 ± 1.65 | 60 | 7.84 ± 1.39 | <0.001 |
| HDL, mmol/L | 92 | 0.73 ± 0.13 | 60 | 0.95 ± 0.23 | <0.001 |
| CFT, μm | 379 | 340.53 ± 149.78 | 191 | 236.39 ± 123.84 | <0.001 |

* The comparison in terms of sex between PDR with and without DON was performed using the Pearson $\chi^2$ test. Other parameters were investigated using an independent-samples *t*-test.

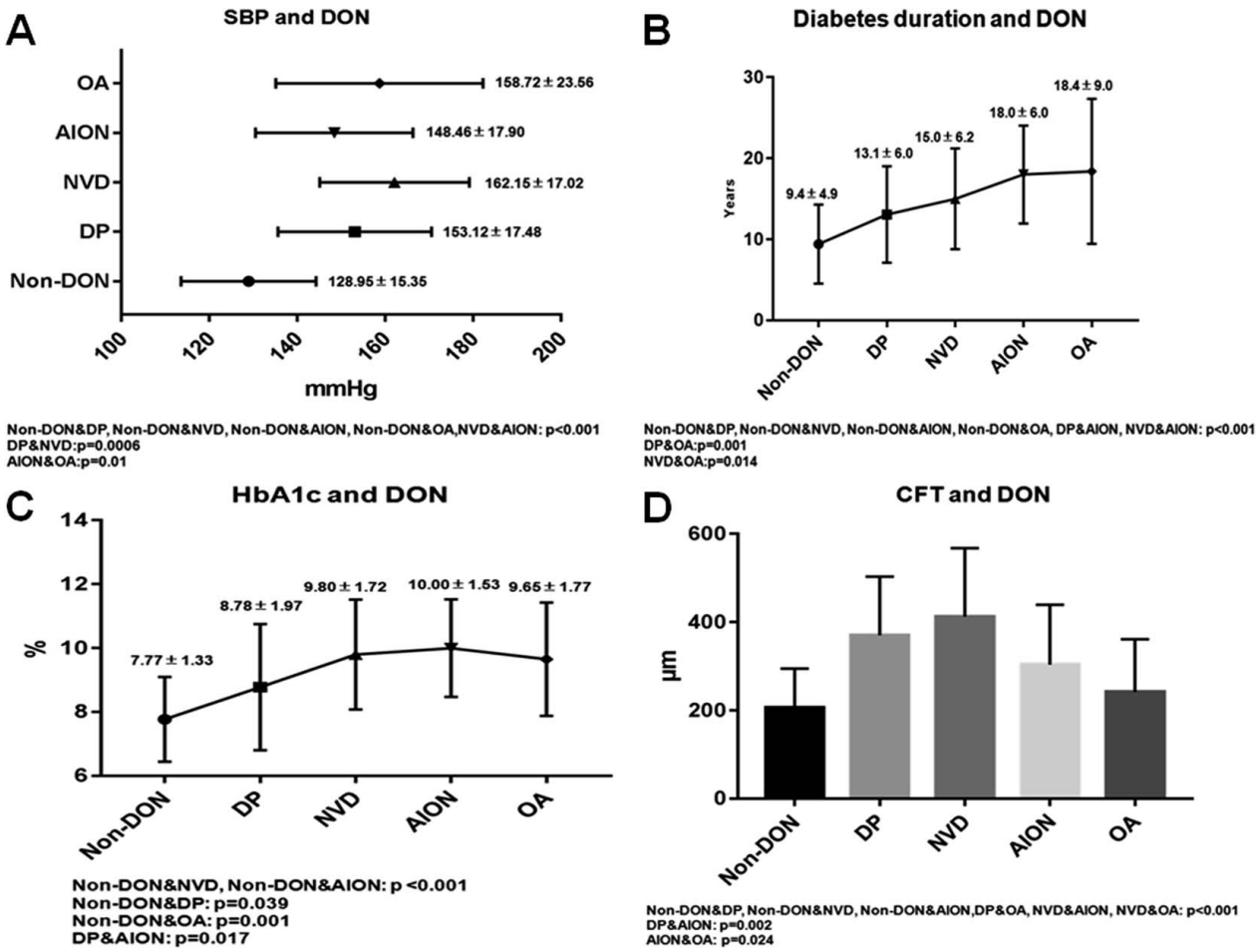


**Figure 2.** Effect of both systemic and ocular parameters on diabetic optic neuropathy. (**A**) Effect of systolic blood pressure on diabetic optic neuropathy incidence. Subjects without DON had a significantly lower SBP than subjects with DON. (**B**) Effect of diabetes duration on diabetic optic neuropathy incidence. Subjects with DON had diabetes for a significantly longer time than subjects without DON. (**C**) Effect of HbA1c levels on diabetic optic neuropathy incidence. The HbA1c values were significantly higher in subjects with DON than in subjects without DON. (**D**) Effect of central foveal thickness (as measured using optical coherence tomography) on DON incidence. The CFT was significantly lower in the non-DON and OA groups than in the DP, NVD, and AION groups. Additionally, CFT in the AION group was significantly lower than that in the DP and NVD groups.

increasing diabetes duration, SBP, CFT, and DR severity (diabetes duration for DP group: $P = 0.002$, DR severity for DP group: $P = 0.015$, all others $P < 0.001$, Table 3). Overall, diabetes duration increased the likelihood of developing DON (ORs: 1.146–1.422), and having NPDR was protective against DON (ORs: 0.024–0.306).

A separate analysis was performed on data from the 304 eyes of 153 subjects that underwent HbA1c and HDL testing. Multiple logistic regression analysis adjusted for age, sex, diabetes duration, SBP, DR severity, CFT, HbA1c, and HDL revealed that the risk for developing DON increased only with increasing HbA1c (NVD: $P = 0.039$; AION: $P < 0.001$; and OA: $P = 0.046$). Overall, an increased HbA1c level increased the risk of developing NVD, AION, and OA (ORs: 1.672–2.158).

## Discussion

The present study examined and compared demographic, systemic, and ocular characteristics of DR patients with and without DON in an effort to identify risk factors associated with developing DON. Varying DON severity was examined using established disease classifications.[7] It is thought that AION and OA are the later stages of DP and NVD. The overall

**Table 3.** Predictors for Developing Diabetic Optic Neuropathy

| DON Type | Parameter | OR | 95% CI | P* |
|---|---|---|---|---|
| DP | Age | 0.941 | 0.895–0.989 | 0.016 |
| | Diabetic duration | 1.146 | 1.050–1.251 | 0.002 |
| | SBP | 1.057 | 1.035–1.079 | <0.001 |
| | CFT | 1.007 | 1.001–1.010 | <0.001 |
| | NPDR | 0.306 | 0.118–0.792 | 0.015 |
| NVD | Age | 0.894 | 0.858–0.932 | <0.001 |
| | Diabetic duration | 1.294 | 1.205–1.389 | <0.001 |
| | SBP | 1.084 | 1.065–1.103 | <0.001 |
| | CFT | 1.007 | 1.005–1.010 | <0.001 |
| | NPDR | 0.024 | 0.005–0.109 | <0.001 |
| AION | Diabetic duration | 1.222 | 1.162–1.284 | <0.001 |
| | SBP | 1.052 | 1.039–1.065 | <0.001 |
| | CFT | 1.004 | 1.002–1.006 | <0.001 |
| | NPDR | 0.102 | 0.058–0.178 | <0.001 |
| Optic atrophy | Age | 0.869 | 0.803–0.941 | 0.001 |
| | Diabetic duration | 1.422 | 1.266–1.596 | <0.001 |
| | SBP | 1.076 | 1.043–1.111 | <0.001 |

* Adjusted for age, sex, diabetes duration, SBP, diabetic retinopathy severity, and CFT.

prevalence of DON in DR patients was 38.4% (163 cases were bilateral cases), with an AION prevalence of 23.8% and a DP prevalence of 3.0%. Our AION prevalence is lower than that previously found by Lee et al.,[8] who reported an overall AION prevalence of 40% in diabetic patients. Given that DM is a major risk factor for AION,[12] diabetic patients should be closely monitored for AION and other forms of DON.

The severity of DR and DME can widely vary between patients and may be accompanied by DP.[13] Optic disc swelling occurs in approximately 0.4% of diabetics, most often in the second and third decades of life.[14] There is no association between DP and tight metabolic control or DR stage when only minimal OA has occurred.[15] However, edema associated with DP has a tendency to resolve, often resulting in no observable permanent sequelae (e.g., OA).[16] Our analyses show that eyes with PDR have a higher prevalence of DON (including DP) than eyes with NPDR. This finding is in agreement with prior studies that found that DP is a risk factor for DR progression.[17]

The idea that DP is a reversible form of AION has been proposed.[10] Classic AION involves a perfusion deficiency (caused directly by hypotension or indirectly by pathology related to capillary vasostasis) that may result in anterior optic nerve head edema. Hypotension-related pathology has been identified in traditionally defined AION. However, in eyes with DP, edema is likely caused by perfusion deficiencies that result from capillary membrane disruption and subsequent interstitial fluid dynamic changes. Edema may then lead to ischemic, compressive, or toxic optic nerve head changes.[5] Our finding that NVD occurred more often in eyes with PDR than in eyes with DP further supports this idea. Eyes with DR accompanied by disc swelling will likely develop retinal ischemia and subsequent neovascularization after disc edema resolution.[14]

The 550 subjects included in the current study had an average diabetes duration of 12.3 ± 6.6 years. Subjects with DP in the current study had a disease duration of 13.1 ± 6.0 years, which is longer than the findings of Bayraktar et al.,[18] who reported an average DM duration of 10.0 ± 8.6 years. The current study also found that diabetes duration progressively increased as DON severity increased (from non-DON to OA). Additionally, the DP and NVD groups had a shorter diabetes duration than the AION and OA groups. Multiple regression analysis in the current study identified diabetes duration as a risk factor for developing DON (OR = 1.146–1.422). This is in agreement with a prior study that showed that diabetes duration is an important factor in DR presence and severity in subjects with AION.[9]

The current study showed that patients with more severe forms of DON tend to be older than those with earlier forms of DON. Mean subject age in the DP group was 52.5 ± 12.8 years, which is in agreement with Bayraktar et al.,[18] who reported a mean subject age of 57.1 ± 8.8 years.[18] Additionally, our DR patients with AION (62.0 ± 9.5 years) were significantly older than our other DR patients. Therefore, our results support the previous finding that AION incidence may be higher in patients older than 67 years.[8] Furthermore, DP predominately occurs in younger patients,[18] but can occur in older type 2 diabetics.[18]

Sex and SBP are other systemic factors that may influence DON occurrence. In the present study, we found that more women developed AION (26.8%) than NVD (7.9%). However, it is reported that no sex predilection exists in AION,[19] as well as NVD. Moreover, estrogen exerts no protective action against AION.[20] Similarly, in our study, sex was not a risk factor for developing DON according to the multiple logistic regression analysis. Additionally, despite the fact that 235 males and 315 females were enrolled, males were still predominant in both AION (73.2%), and NVD groups (92.1%). Lee et al.[8] reported that male diabetic patients were 32% more likely to develop AION than female diabetic patients. The authors speculated that smoking may be an important risk factor for males with a high prevalence of AION and NVD in this study. To our knowledge, cigarettes contain toxic metals, such as Pb, Ni, Cd, and As, which disrupt glucose uptake and alter the related molecular mechanism of glucose regulation. There was also a positive association between Cd and plasma levels of glycated hemoglobin.[21] Therefore, smoking can aggravate DR, leading to high occurrences of AION and NVD in males. However, we did not survey smoking status in the present study. We will consider this in further research.

SBP was significantly higher in our subjects with DON (154.12 ± 12.04 mm Hg) than in those without DON (128.95 ± 15.35 mm Hg). This finding is in agreement with another study that found hypertension to be a risk factor for AION in diabetic patients.[22]

Plasma HbA1c and HDL levels may influence the development of DON. Subjects in the current study had a mean HbA1c of 8.42 ± 1.72% (68.58 ± 18.82 mmol/mol), indicating a moderate level of metabolic control. Poor metabolic control and abrupt tightening of glycemic control (e.g., during pregnancy and upon insulin therapy initiation) may be associated with optic neuropathy.[18] In agreement, our subjects with DON had significantly higher HbA1c levels than our subjects without DON. This was particularly true in our subjects with NPDR and PDR. Moreover, AION subjects had significantly higher HbA1c levels than DP subjects. An acute decrease in HbA1c, along with a small cup-to-disc ratio, may put a patient at risk for developing DP.[3] Additionally, DR can worsen with intensive glycemic control,[2,23] which is thought to result from closure of small retinal vessels that were already narrowed in patients with severe diabetes.[2] In contrast, papillopathy often improves when glucose levels temporarily return to normal.[1] This study also showed that HDL was significantly lower in subjects with DON than in subjects without DON, which was similar in the PDR with or without DON patients. Particularly, AION subjects had the highest HDL value compared with the other three type of DON. Similarly, Sharma et al.[22] also found that hyperlipidemia is a risk factor for AION in diabetic patients. Further research is needed to better understand the influences of both low-density lipoprotein and HDL on DON.

Ocular factors, including CFT and DR severity, influenced DON incidence. Mean CFT was 370.16 ± 133.2 μm in the DP group, which was significantly greater than that of the AION, OA, and non-DON groups. This finding is consistent with the theory that DME may be present with DP,[18,24] along with NPDR or PDR.

Diabetic patients have a greater risk of developing AION.[25,26] The current study showed that an increase in age, diabetes duration, SBP, and a larger CFT elevated the risk of developing DP, NVD, and OA. Additionally, the risk of developing DP, NVD, and AION increased with greater diabetes duration, SBP, CFT and DR severity. However, HbA1c was also an important factor, with elevated levels increasing the risk of developing NVD, AION, and OA. The mechanisms underlying these risk factors are not completely understood. However, DR and hypertensive retinopathy are characterized by endothelial damage, a leaky blood–retinal barrier, vascular occlusion, and ischemia, all of which eventually contribute to neovascularization.[27] Therefore, ischemic optic neuropathy may be associated with DR and hypertensive retinopathy because of a diffusely impaired ocular microcirculation, including within the optic nerve. Thus, the presence of these degenerative eye conditions may be indicative of more widespread ocular circulatory abnormalities.[28]

Our study had several limitations related to its retrospective design. Some known risk factors (e.g., a small cup-to-disc ratio, which is a known risk factor for nonarteritic anterior ischemic optic neuropathy[18]) were not included in our analyses because these data were not present in medical records. Additionally,

only 153 of 550 subjects (27.8%) had available serum HbA1c and HDL measurements. Moreover, a hospital-based patient population had its inherent limitations, resulting in enrolling more PDR patients in our study. Therefore, future prospective studies should contain the same data for all subjects to further evaluate and understand DON risk factors. Natural population epidemiology should be carried on a large scale. Even with these limitations, our study offers insight into DON.

In spite of our population being hospital-based patients, the results from the present study could also be extrapolated to the general diabetic patient population. We found that similar risk factors influence both DR and DON simultaneously. For example, increased age, diabetes duration, SBP, CFT, and DR severity were risk factors for DON, and increased HbA1c was a risk factor for NVD, AION, and OA. No comprehensive investigation has reported on the prevalence of DON and its risk factors in Chinese DR patients previously. Hence, we believe that the results from the present study have important clinical significance for the general diabetic patient population.

This is the first epidemiologic study on the prevalence and distribution of risk factors for DON in Chinese DR patients. We found that PDR subjects had a higher DON incidence compared with NPDR subjects. Additionally, HDL was significantly higher in subjects without DON than in subjects with DON, the same as PDR with DON and without DON, indicating that HDL may be a protective factor for DON. Our results also strengthen the argument that increased age, diabetes duration, SBP, CFT, DR severity, and HbA1c are all risk factors for developing DON in patients with DR. Therefore, in clinical practice, it is important to recognize and control these risk factors to delay the occurrence of DON.

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