Al-Rafidain J Med Sci. 2026;11(1):185-191.
DOI: https://doi.org/10.54133/ajms.v11i1.3129

AJMS

Online ISSN (3219-2789)

Research Article

Correlation of Isolated Masked Nocturnal Hypertension with Retinopathy in Diabetic Patients

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Received: 26 May 2026; Revised: 10 July 2026; Accepted: 17 July 2026

Abstract

Background: The most common cause of visual impairment in the working-age population is diabetic retinopathy. Hypertension is thought to directly or indirectly cause 35% to 75% of diabetes complications. The prevalence of masked hypertension and masked nocturnal hypertension is higher in diabetic patients. In those who have diabetes mellitus, nocturnal blood pressure appears to be more relevant for the development of diabetic retinopathy. ***Objective***: To assess the relationship between isolated masked nocturnal hypertension and retinopathy in diabetic patients. ***Methods***: An observational case-control study was conducted on 234 individuals with diabetes; 117 of them have retinopathy, while the remaining do not. All patients were assessed for hypertension by measuring blood pressure in the office and through 24-hour ambulatory blood pressure monitoring. ***Results***: Twenty-three percent of all assessed patients had masked hypertension. Isolated masked nocturnal hypertension (IMNH) was detected in 15.4% of those with retinopathy, while it was 6% for those without retinopathy. There was a significant relationship between IMNH and the severity of retinopathy. IMNH was more prevalent in those aged 40 years and older, as well as in overweight and obese patients. ***Conclusions***: The current study indicated that diabetic patients with retinopathy exhibited a higher prevalence of masked nocturnal hypertension than those without retinopathy. This result could indicate that masked nocturnal hypertension plays a contributory role in the development of retinopathy.

Keywords: Ambulatory blood pressure monitoring; Diabetes mellitus; Masked nocturnal hypertension; Retinopathy.

العلاقة بين ارتفاع ضغط الدم الليلي المقنع المعزول مع اعتلال الشبكية لدى مرضى السكري

الخلاصة

الخلفية: السبب الأكثر شيوعا لضعف البصر بين السكان في سن العمل هو اعتلال الشبكية السكري. يعتقد أن ارتفاع ضغط الدم يسبب بشكل مباشر أو غير مباشر ما بين 35٪ إلى 75٪ من مضاعفات السكري. انتشار ارتفاع ضغط الدم المخفي وارتفاع ضغط الدم الليلي المقنع أعلى لدى مرضى السكري. في الأشخاص الذين يعانون من مرض السكري، يبدو أن ضغط الدم الليلي أكثر أهمية لتطور اعتلال الشبكية السكري. **الهدف**: تقييم العلاقة بين ارتفاع ضغط الدم الليلي المقنع المعزول واعتلال الشبكية لدى مرضى السكري. **الطرائق**: أجريت دراسة حالة وشاهد رصدي على 234 شخصا مصابا بالسكري؛ 117 منهم يعانون من اعتلال الشبكية، بينما الباقون لا. تم تقييم جميع المرضى لارتفاع ضغط الدم من خلال قياس ضغط الدم في العيادة ومن خلال مراقبة ضغط الدم على مدار 24 ساعة. **النتائج**: كان 23 بالمئة من جميع المرضى الذين تم تقييمهم لديهم ارتفاع ضغط دم مخفي. تم اكتشاف ارتفاع ضغط الدم الليلي المقنع المعزول (IMNH) لدى 15.4٪ من المصابين باعتلال الشبكية، بينما كان 6٪ لمن لا يعانون من اعتلال الشبكية. كان هناك علاقة كبيرة بين IMNH وشدة اعتلال الشبكية. كان مرض IMNH أكثر انتشارا بين من هم في سن الأربعين فأكثر، وكذلك لدى المرضى الذين يعانون من زيادة الوزن والسمنة. **الاستنتاجات**: أشارت الدراسة الحالية إلى أن مرضى السكري المصابين باعتلال الشبكية أظهروا انتشارا أعلى لارتفاع ضغط الدم الليلي المخفي مقارنة بمن لا يعانون من اعتلال الشبكية. قد تشير هذه النتيجة إلى أن ارتفاع ضغط الدم الليلي المخفي يلعب دورا مساهما في تطور اعتلال الشبكية.

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Article citation: Mustafa HM, Mahwi TO, Rashid ZG. Correlation of Isolated Masked Nocturnal Hypertension with Retinopathy in Diabetic Patients. *Al-Rafidain J Med Sci*. 2026;11(1):185-191. doi: https://doi.org/10.54133/ajms.v11i1.3129

INTRODUCTION

The most common cause of visual impairment in the working-age population is diabetic retinopathy (DR) [1]. Furthermore, among those aged 20-74 years, it is a major cause of new cases of blindness [2]. 30% of diabetic patients will develop retinopathy [3]. Both the duration of diabetes and severity of hyperglycemia are major risk factors for the development of DR [4]. An increase in BP is also a risk factor for the development and progression of DR [5]. A survey done from 2005 to 2008 shows that the prevalence of hypertension in diabetic patients is twice that of the general population (57.3% vs. 28.6%) [6]. Furthermore, the prevalence of uncontrolled and undiagnosed hypertension is higher in diabetic cases [7]. Diabetic cases need more antihypertensives (3 or more medications) if compared to non-diabetics (31.6% versus 17.8%) [8]. Hypertension is regarded as a major risk factor for the development of macrovascular and microvascular complications in diabetes [9]. Researchers estimate that hypertension (HTN) directly or indirectly contributes to 35% to 75% of diabetes complications [10]. Undetected hypertension in diabetic patients is associated with faster end-organ damage compared to those who have no diabetes [11]. The most commonly applied and popular way to measure and monitor BP is by using office BP monitoring. Many studies indicate that ambulatory BP monitoring (ABPM) is better at evaluating BP variability than office measurement [12].

According to the 2018 Guidelines for the management of arterial HTN from the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH), for better risk stratification of HTN, it is better to perform ABPM at least once [13]. To prevent the complications of hypertension, it is more ideal to control the diurnal and nocturnal variability and not only the average daily BP [14]. Studies indicate that ABPM is more sensitive to predicting end-organ damage if compared to office monitoring [15]. ABPM is considered normal if the 24-hour average blood pressure is less than 130/80 mmHg, the average blood pressure during awake times is less than 135/85 mmHg, and the average blood pressure at night is less than 120/70 mmHg [16]. Masked HTN is categorized into three categories: the overall masked HTN when office BP is normal but average 24 h ABPM readings are ≥ 130/80 mmHg [8]; the isolated daytime masked HTN when office BP is normal but daytime ABPM readings are ≥ 135/85 mmHg [17]; and the isolated nocturnal masked HTN when office BP is normal but nighttime ABPM readings are ≥ 120/70 mmHg [18]. Li *et al.* in 2007 first described isolated nocturnal hypertension (INH) [19]. The prevalence of INH is not well documented. In Australia and China, in those patients for whom the prevalence of INH among normotensive patients was 14.4%, to be normotensive, the prevalence of INH was 14.4% and 13.2%, respectively [20]. The prevalence of INH among Black Americans was 19.1% [21], while in the Korean population it was documented to be 18.1% [22]. The risk of cardiovascular mortality and morbidity is higher in those patients with INH [19]. Studies indicate that the risk of target organ damage like left ventricular hypertrophy, retinopathy, and proteinuria is higher with nighttime HTN [23]. In the general population, fatal cardiovascular events are better predicted from nighttime HTN than daytime, and as the level of nocturnal BP increases, the risk of cardiovascular death also rises [24]. A “non-dipping” (nocturnal SBP fall <10% of the daytime SBP value) is common in type 2 and type 1 diabetes and is associated with endothelial dysfunction, carotid atherosclerosis, resistant hypertension, and target organ damage [25]. The prevalence of masked HTN and masked INH is higher in diabetic patients, in contrast to white coat hypertension, which is less prevalent in diabetics [8]. The explanation for why masked INH is more common in diabetic patients is not well understood but may be due to a reduction in the parasympathetic nervous activity, and higher norepinephrine plasma levels suggest that the sympathetic drive is increased, as well as autonomic nervous dysfunction and disrupted variation of the sympathetic and parasympathetic balance [26]. The prevalence of retinopathy, nephropathy, and coronary heart disease is increased in type 2 DM patients with masked HTN; also, the risk of end-organ damage increases [27]. However, comparing masked HTN to isolated masked nocturnal HTN as a more potent risk factor for the development of complications of diabetes is not known [28]. Hyperglycemia increases the chance of retinal damage from hypertension, possibly due to the impairment of normal retinal autoregulation, so retinal ischemia due to shearing damage to the retinal capillary is a fundamental determinant of DR [29]. The progression of retinopathy in patients with T1DM is shown to be greatly influenced by nocturnal HTN [2]. In those who have type 2 DM, the nocturnal BP appears to be more relevant for the development of diabetic retinopathy [30]. The current study aims to assess the relationship between isolated masked nocturnal hypertension and retinopathy in diabetic patients.

METHODS

Study design and setting

In this observational case–control study, 234 diabetic individuals were examined, comprising 227 with type 2 diabetes and 7 with type 1. Among these, 117 participants had retinopathy, while the remaining 117 did not. The participants were systematically recruited from the Endocrinology and Diabetic Clinic at Shar Teaching Hospital in Sulaymaniyah, Iraq, over the period from February to December 2025.

Inclusion criteria

To be qualified, patients needed to be at least 18 years old, have had diabetes for a minimum of 5 years, and have no history of hypertension or treatment with antihypertensive medication. Hypertension was characterized by an office systolic blood pressure of 140 mmHg or higher and/or a diastolic blood pressure of 90 mmHg or higher [31].

Exclusion criteria

Age <18 years, diabetes duration <5 years, pregnancy, or a prior diagnosis of hypertension.

Sample size calculation

Using G*Power (version 3.1.9.7), the sample size was calculated based on a medium effect size (Cohen’s d = 0.5), with α set at 0.05 and power at 0.80, resulting in 94 participants needed for each group. To enhance reliability and facilitate subgroup analyses, a total of 234 patients were enrolled.

Outcome measurements

Diabetes was identified based on the 2024 guidelines set by the American Diabetes Association. Blood pressure evaluation involved both standardized office readings and 24-hour ambulatory monitoring using the Spacelabs 90217A device. Patients were deemed normotensive if both office and ambulatory blood pressure readings were within normal limits. Conversely, they were considered to have masked hypertension if the office blood pressure was normal, but the ambulatory readings were elevated. Masked hypertension was further divided into overall, isolated daytime, or isolated nocturnal categories. Retinopathy was evaluated by a qualified

ophthalmologist using dilated fundus examination and categorized into five grades: no retinopathy, background, preproliferative, proliferative, and maculopathy [32]. Information on demographics and clinical characteristics, such as age, gender, smoking habits, alcohol consumption, type and duration of diabetes, and BMI, was gathered through a structured interview process. Laboratory tests comprised measurements of HbA1c, serum creatinine, and the urine albumin-to-creatinine ratio. The glomerular filtration rate (GFR) was determined using the Cockcroft–Gault equation. Diabetes was classified as controlled when HbA1c levels were below 7%.

Ethical consideration

The study was approved by the Medical Research Scientific and Ethics Committee of the Kurdistan Higher Council of Medical Specialties (Certificate ID: 1412; 14/4/2025), and all participants provided written informed consent.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation (SD), minimum, maximum, and 95% confidence intervals (95% CI), whereas categorical variables were presented as frequencies and percentages (n, %). The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to assess the normality of continuous variables. An independent samples t-test, Mann–Whitney U test, chi-square test, and Fisher's exact test were employed in this study. All tests were two-sided with statistical significance set at $p< 0.05$.

RESULTS

As presented in Table 1, the mean age of the participants with retinopathy was 56.54 ± 10.64 years and 53.49 ± 13.07 years for those without retinopathy. Equally, 53% of enrolled patients were females in both groups. 64% of the retinopathy arm had never smoked, compared to 68% of patients without retinopathy.

Table 1: Sociodemographic characteristics of diabetic patients with and without retinopathy

Sociodemographic	With Retinopathy (n=117)	Without Retinopathy (n=117)	Total (n=234)
Age (year)			
95%CI	54.59-58.49	51.09-55.88	53.47-56.56
Mean±SD	56.54±10.64	53.49±13.07	55.01±11.99
18-40	11(9.4)	20(17.09)	31(13.25)
41-60	67(57.26)	64(54.7)	131(55.98)
>60	39(33.33)	33(28.21%)	69(30.77)
Gender			
Female	62(53)	62(53)	124(53)
Male	55(47)	55(47)	110(47)
Smoking status			
Never smoked	76(64.96)	80(68.38)	156(66.67)
Smoker + ex-smoker	41(35.04)	37(31.62)	78(33.33)
Alcoholic status			
Drinker	10(8.5)	21(17.90)	31(13.2)
Non-drinker	107(91.5)	96(82.10)	203(86.8)
BMI (kg/m^2)			
95%CI	26.87-28.14	26.16-27.65	26.72-27.69
Mean±SD	27.50±3.46	26.91±4.06	27.21± .78
Underweight	0(0.0)	1(0.9)	1(0.4)
Normal weight	25(21.4)	37(31.62)	62(26.5)
Overweight	63(53.8)	54(46.2)	117(50.)
Obese	29(24.8)	25(21.37)	54(23.08)

68% of patients without retinopathy had never smoked. 91% of retinopathy patients and 82% of non-retinopathy patients did not drink alcohol. 78.6% of patients who had retinopathy were either overweight or obese, which was higher than that of those without retinopathy (67.57%). As shown in Table 2, among the 234 individuals with diabetes who were included in the study, only 9 patients had type 1 diabetes. The mean duration of diabetes was approximately 11 years in both categories. Uncontrolled diabetes was observed in 66% and 61% for those with retinopathy and without retinopathy, respectively. A high urine albumin/creatinine ratio was more commonly detected in diabetic patients with retinopathy (35%) compared to those without retinopathy (23%). Higher prevalence of low GFR was identified among patients with retinopathy (56%). Data obtained from the 24-hour ABPM of all assessed patients showed that 55 patients (23%) had masked hypertension (including isolated masked daytime, isolated masked nocturnal, and combined masked daytime and nocturnal hypertension) (Table 3); 10.7% of all evaluated patients had isolated masked nocturnal hypertension. True normotension was detected more commonly in patients without retinopathy (82%) compared to 70% for those with retinopathy (p= 0.021). A statistically significant difference was seen between the two categories regarding the identification of isolated masked nocturnal hypertension, which was 15% in the retinopathy group and 6% in the non-retinopathy group (p= 0.02) (Table 3). As demonstrated in Table 4, among the 117 participants who were diagnosed with

retinopathy, true normotension was the most frequent ABPM pattern (70.1%) and was significantly more common in patients with background retinopathy compared with more advanced retinopathy stages ($p<$ 0.001).

Table 2: Clinical and biochemical characteristics of individuals with diabetes with and without retinopathy

Clinical characteristics	With retinopathy (n=117)	Without retinopathy (n=117)	Total (n=234)
Type of DM			
Type 1	3(2.6)	6(5.1)	9(3.8)
Type 2	114(97.4)	111(94.9)	225(96.2)
Duration of DM (year)			
95%CI	10.72-12.62	10.18-12.35	10.75-12.18
Mean ± SD	11.67±5.2	11.27±5.91	11.47±5.56
5-10	60(51.28)	71(60.68)	131(55.98)
11-15	36(30.77)	23(19.66)	59(25.21)
16-20	12(10.26)	15(12.82)	27(11.54)
>20	9(7.69)	8(6.84)	17(7.26)
HbA1c (%)			
Controlled	39(33.30)	45(38.5)	84(35.9)
Uncontrolled	78(66.70)	72(61.5)	150(64.1)
UACR (mg/g)			
95%CI	70.42-150.43	34.28-78.06	60.39-160.11
Mean ± SD	110.33±217.95	56.17±119.55	83.25±177.49
Normal UACR	75(64.1)	90(76.9)	165(70.5)
High UACR	42(35.9)	27(23.1)	69 (29.5)
GFR (mL/minute/1.73 m²)			
95%CI	82.79-88.39	86.91-91.64	85.60-89.27
Mean±SD	85.59±15.27	89.27±12.92	87.43±14.23
Low GFR	66(56.4)	49(41.9)	115(49.1)
Normal GFR	51(43.6)	68(58.1)	119(50.9)

UACR: Urine albumin/creatinine ratio; HbA1c: Glycated haemoglobin; GFR: Glomerular filtration rate.

Table 3: Ambulatory blood pressure monitoring phenotypes in individuals with diabetes with and without retinopathy

ABPM	With Retinopathy (n=117)	Without Retinopathy (n=117)	Total (n=234)	*p*-value
Isolated masked daytime HTN	7(6.0)	5(4.3)	12(5.1)	0.553
Isolated masked nocturnal HTN	18(15.4)	7(6.0)	25(10.7)	0.02
Masked daytime and nocturnal HTN	10(8.5)	8(6.8)	18(7.7)	0.624
True normotension	82(70.1)	97(82.9)	179(76.5)	0.021

ABPM: Ambulatory blood pressure monitoring; n: Number; HTN: Hypertension. The data were analysed using the chi-square test.

Table 4: Ambulatory blood pressure monitoring phenotypes across retinopathy categories

ABPM	Retinopathy categories					*p*-value
	Background 51(43.59)	Pre-proliferative 32(27.35)	Proliferative 26(22.22)	Maculopathy 8(51.28)	Total 117(100)	
Isolated masked daytime HTN	2(3.9)	1 (3.10%)	4 (15.40%)	0 (0.00%)	7(6.0)	0.156
Isolated masked nocturnal HTN	4(7.8)	10(31.3)	2 (7.70%)	2 (25.00%)	18(15.4)	<0.001
Masked daytime and nocturnal HTN	1(2.0)	6(18.8)	3 (11.50%)	0 (0.00%)	10(8.5)	0.05
True normotension	44(86.3)	15(46.9)	17 (65.40%)	6 (75.00%)	82(70.1)	<0.001

ABPM: Ambulatory blood pressure monitoring; HTN: Hypertension. The data were analysed using the chi-square test.

Isolated masked nocturnal hypertension was present in 15.4% of all retinopathy categories, and a significant association was noted with retinopathy severity, being particularly prevalent in pre-proliferative (31.3%) and maculopathy (25.0%) groups ($p<$ 0.001). Masked hypertension involving both daytime and nocturnal periods was observed in 8.5% of patients and demonstrated borderline statistical significance across retinopathy categories ($p=$ 0.050). In contrast, isolated masked daytime hypertension was detected in the minority of patients (6.0%) and did not differ significantly among retinopathy stages ($p=$ 0.156). The interpretation of the data obtained from Table 5 showed that the prevalence of isolated masked nocturnal hypertension was more commonly observed among those patients aged 40 years and older ($p=$ 0.042). Isolated masked nocturnal hypertension was mostly detected in those individuals with diabetes who never smoked compared to smokers and ex-smokers ($p=$ 0.05). Body mass index was significantly associated with the observation of isolated masked nocturnal hypertension, as the majority of those patients diagnosed to have isolated masked nocturnal hypertension were either overweight (66.7%) or obese (27.8%) ($p=$ 0.006). As previously demonstrated in Table 2, among the 234 enrolled patients, only 9 patients had type 1 diabetes. Based on this finding, we can derive the concept that the detection of isolated masked nocturnal hypertension will be more prevalent among type 2 diabetic patients (94%) (Table 6). Gained from Table 6 was that the recognition of isolated masked nocturnal hypertension will increase with the duration of diabetes, especially 10 years after

diagnosis. The prevalence of isolated masked nocturnal hypertension was more common in those patients with uncontrolled diabetes ($p< 0.001$). A non-statistically significant relationship was observed between the level of urine albumin/creatinine ratio and the occurrence of isolated masked nocturnal hypertension; in contrast, a highly statistically significant relationship was detected between low GFR and isolated masked nocturnal hypertension among those individuals with diabetes who were diagnosed with retinopathy.

Table 5: Sociodemographic characteristics of individuals with diabetes with retinopathy among those with isolated masked nocturnal hypertension (n=18)

Variables	Isolated masked nocturnal HTN in patients with retinopathy (n=18)	*p*-value
Age (year)		
18-40	1(5.56)	
41-60	9(50)	0.042
>60	8(44.44)	
Smoking status		
Never smoked	13(72.22)	0.05
Smoker + ex-smoker	5(27.78)	
Alcoholic status		
Non-drinker	18(100)	NA
Drinker	0(0.0)	
BMI (kg/m²)		
Underweight	0(0.0)	
Normal weight	1(5.56)	0.006
Overweight	12(66.67)	
Obese	5(27.78)	

n: Number; NA: Not statistically applicable. Categorical variables like smoking and alcoholic status were analysed using Fisher's exact test, and all other categorical variables were analysed using the chi-square test.

Table 6: Clinical characteristics of individuals with diabetes with retinopathy among those with isolated masked nocturnal hypertension (n=18)

Variables	Isolated masked nocturnal HTN in patients with retinopathy (n=18)	*p*-value
Type of DM		
Type 1	1(5.56)	<0.001
Type 2	17(94.44)	
Duration DM (year)		
5–10	5(27.78)	
11–15	8(44.44)	0.135
16–20	1(5.56)	
>20	4(22.22)	
HBA1c		
Controlled	2(11.11)	<0.001
Non-controlled	16(88.89)	
UACR (mg/g)		
Normal UACR	9(50)	1.0
High UACR	9(50)	
GFR (mL/minute/1.73 m²)		
Low GFR	14(77.78)	0.018
Normal GFR	4(22.22)	

n: Number; UACR: Urine albumin /creatinine ratio; HbA1c: Glycated hemoglobin; GFR: Glomerular filtration rate. Categorical variables like type of DM and HBA1c were analysed using Fisher's exact test, and all other categorical variables were analysed using the chi-square test.

DISCUSSION

This study investigated the association between isolated masked nocturnal hypertension (IMNH) and diabetic retinopathy complications in both type 1 and type 2 diabetes. While researchers have established a strong link between hypertension and diabetic retinopathy, few studies have specifically examined the impact of masked nocturnal hypertension. In the current study, among the 234 patients, 23% of them had masked hypertension, and 10.7% of these had IMNH. Rodrigues *et al*. reported masked hypertension in 14% of type 1 diabetic patients, with 23% showing nocturnal hypertension [33]. Wijkman *et al*. found nocturnal hypertension in 30% of clinically normotensive type 2 diabetics [7]; however, in a study done by Marchesi *et al., a* higher rate was detected, which reached 47% [34]. In the present study, we recorded that IMNH was more common in individuals with diabetes who had retinopathy compared to those without retinopathy. This finding is in concordance with a study done by Rodrigues *et al*. in patients with type 1 diabetes [33], and comparable results were observed by Najafi *et al*. in type 2 diabetic patients [10]. A significant association was observed between retinopathy severity and IMNH, particularly in pre-proliferative retinopathy and maculopathy. These findings are consistent with a study done by Klein *et al*., which showed that nighttime systolic hypertension was associated with the severity of retinopathy [35]. This association may be explained by autonomic dysfunction and impaired retinal autoregulation, leading to increased nocturnal retinal blood flow and subsequent microvascular damage [36]. In the current study, we observed that IMNH were mostly

detected among those patients who are 40 years and older and among those who had diabetes for 10 years and more; these findings are in concordance with a study done by Klein *et al.* [35]. Most patients with IMNH were overweight or obese, a pattern also reported by Mateo *et al.* [37]. There was a statistically significant relation between IMNH and uncontrolled diabetes, and this finding is consistent with the same observation by Rodrigues *et al.* [33]. Although some studies record a significant relationship between nocturnal hypertension and microalbuminuria [37], no significant association was found between IMNH and microalbuminuria; however, IMNH was significantly related to reduced GFR, consistent with Rodrigues *et al.* [33].

Strengths and Limitations

This study used a case-control design with equal groups of diabetic patients with and without retinopathy, allowing direct comparison. The use of both office blood pressure measurement and 24-hour ambulatory monitoring improved the detection of masked and isolated nocturnal hypertension. On the other hand, the single-center observational case-control design limits generalizability and does not allow causal inference. The relatively modest sample size, tiny number of type 1 diabetes patients, and potential residual confounding from factors such as diabetes duration, glycemic control, and renal status may have influenced the associations.

Conclusions

Diabetic patients with retinopathy exhibited a higher prevalence of masked nocturnal hypertension than those without retinopathy. This result could indicate that masked nocturnal hypertension plays a contributory role in the development of retinopathy and supports the use of ambulatory blood pressure monitoring in all diabetic patients who have normal blood pressure readings in the office to detect masked hypertension, especially nocturnal, and for better risk stratification.

Conflict of interests

The authors declared no conflict of interest.

Funding source

The authors did not receive any source of funds.

Data sharing statement

The datasets generated and/or analyzed during the current study are not publicly available due to ethical and privacy restrictions but are available from the corresponding author upon reasonable request.

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