

Assessment for the Correlation Between Diabetic Retinopathy and Metabolic Syndrome: A Cross-Sectional Study

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Purpose: In this study, we explored the correlation between diabetic retinopathy (DR) and metabolic syndrome (MetS) among diabetes mellitus (DM) patients.

Methods: Logistic regression analysis was utilized to test the effects of MetS and its indicators on the incidence of DR and vision-related functional burden. The spline smoothing functions of continuous indicators of MetS were used to establish the logistic generalized additive model (GAM). The effective degree of freedom (EDF) =1 was served as a sign of linear relationship. EDF>1 was a sign of a more complex association between MetS and DR.

Results: The proportion of difficulties of looking for objects on the crowded shelves in the DR group was higher than that in the non-DR group (19.40 vs 12.10, $P<0.05$). Elevated fasting glucose (Glu) and blood pressure levels were related to the vision-related functional burden. The risk of DR development increased by 6% [95% confidence interval (CI): 1.03–1.09, $P<0.001$] and 1% (95% CI: 1.01–1.02, $P=0.004$) per 1 unit increase in Glu and systolic blood pressure (SBP) of DM patients, respectively. In the univariate GAM, Glu had a linear effect on DR (EDF=1, $P<0.001$) with a positive correlation after controlling SBP. And there was a nonlinear correlation between SBP and DR after controlling Glu (EDF=2.44, $P=0.024$).

Conclusion: Both Glu and blood pressure were associated with the occurrence of DR and vision-related functional burden. Controlling the levels of Glu and blood pressure may reduce the risk of DR and vision loss among DM patients.

Keywords: diabetic retinopathy, generalized additive model, glucose, blood pressure

Introduction

Diabetic retinopathy (DR), a common microvascular complication of diabetes mellitus (DM), is a major cause of blindness among adults of working age.¹ It manifests the progressive changes in microvasculature, leading to retinal ischemia, neovascularization, altered retinal permeability and macular edema, which has prominent impacts on the life quality and functional capabilities of humans.^{2,3} A previous report predicted that the diagnosis of DR is gradually increased between 2005 and 2050, up to 16 million in USA.⁴ Epidemiologic data have shown that long-term diabetes, poor blood glucose control and hypertension are concerned risk factors for the onset of DR.⁵ It is necessary to identify risk factors affecting the occurrence of DR for developing clinical management strategies to decline disease progression and prevent visual loss.

Metabolic syndrome (MetS), a complex syndrome of metabolic disorders, manifests a pathological status of metabolic disorder of protein, fat and

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carbohydrate in human body, first proposed by Reaven in 1988.⁶ It contains a cluster of risk factors, such as hypertension, dyslipidemia, abdominal obesity and glucose intolerance, which are associated with cardiovascular and cerebrovascular diseases and DM.^{7–10} Approximately one in four adults suffer from MetS worldwide,¹¹ and the mortality of these individuals is twice as high as people without MetS.¹² Studies showed that the presence of MetS was a predictive indicator for cardiovascular disease in type 2 diabetes patients as well as in non-diabetics.^{12,13} In addition, the correlation between MetS and microvascular complications has been reported, such as DR.

Herein, we utilized the National Health and Nutrition Examination Survey (NHANES) database to investigate the association between DR and MetS in patients with DM by generalized additive model (GAM).

Materials and Methods

Patients

We extracted the data from NHANES (2005–2008) which is a cross-sectional survey for health and nutritional status of the US civilian and non-institutionalized population conducted by National Center of Health Statistics (NCHS) and Centers for Disease Control and Prevention (CDC).¹⁴ Subjects were randomly screened based on a complex, stratified multi-stage cluster sampling design. The information collection was carried out by interviews, and corresponding examinations and assessments were conducted in the mobile examination center (MEC). Additional information was available at <http://www.cdc.gov/nchs/nhanes.htm>. A total of 450 patients with DM were included aged ≥ 40 years, excluding gestational DM. The definition of diabetes was self-reports from patients or diagnoses from doctors or health professionals.

Diagnostic Criteria

DR was diagnosed by the presence of retinal microaneurysms or retinal blot hemorrhages using an ophthalmic digital imaging system. The severity of DR was assessed according to NHANES Grading Protocol. The detailed classifications were as follows: no retinopathy, mild non-proliferative retinopathy (NPR) and severe NPR/proliferative diabetic retinopathy (PDR), which was defined as “OPDURL4” in the NHANES database.¹⁵

In accordance with the Joint Scientific Statement Harmonizing the Metabolic Syndrome,¹⁶ MetS was defined as the presence of 3 or more of the following

features: hypertension, hypertriglyceridemia, low high-density lipoprotein (HDL), elevated fasting glucose, and abdominal obesity. Elevated blood pressure was defined as systolic blood pressure (SBP) ≥ 130 mmHg/diastolic blood pressure (DBP) ≥ 85 mmHg, or self-reported current antihypertensive drug use. Hypertriglyceridemia was identified based on triglyceride (TG) ≥ 150 mg/dL. Low HDL was a level of < 40 mg/dL in men or < 50 mg/dL in women. Elevated fasting glucose (Glu) was defined as Glu ≥ 100 mg/dL, or self-reports of current insulin or oral hypoglycemic drug use. Abdominal obesity was defined as waist > 88 cm for female and > 102 cm for male.

Functional Difficulties of Vision

According to the self-reported visual functional difficulties, the vision-related functional burden was classified by causes of reading (Q_1), close-up work (Q_2), looking for objects on the crowded shelves (Q_3), walking down the steps, stairs or curbs (Q_4), noticing objects to the side during ambulation (Q_5) and driving (Q_6). The Likert scale was used to identify the functional difficulties of patients' vision in each category, which was divided into 5 classifications including no difficulty, little difficulty, moderate difficulty, extreme difficulty and incapability of doing due to eyesight. If participants had moderate or extreme difficulties, or could not do activities, they would be categorized as having difficulties in a specific task.

Statistical Analysis

Statistical analyses were performed using R software 3.6.1. Continuous data were presented as the mean \pm standard deviation ($\bar{X} \pm s$) or $[M(Q_{25}, Q_{75})]$ and analyzed by *t*-test or Mann–Whitney *U*-test. Logistic regression was used to analyze the effect of MetS and its indicators on DR. GAM is an extension of the generalized linear model which allows the evaluation for the curvilinear relationship between outcomes and predictors. The normality of residuals, homoscedasticity, and residual symmetry was used to assess the model assumptions. The spline smoothing functions of continuous indicators of MetS were used to establish the Logistic GAM. The significant variables of univariate analysis were included in GAM to conduct multivariate analysis, which was utilized to analyze nonlinear influencing factors of MetS indicators on DR. The values of effective degree of freedom (EDF) output showed the degree of the smooth curvature. EDF=1 was served as a sign of linear relationship. EDF > 1 was a sign of a more complex association

Table 1 The Baseline Characteristics of Patients with DM

Variables	Total (n=450)		Male (n=210)		Female (n=240)	
	Normal (n=28)	DR (n=170)	Normal (n=121)	DR (n=89)	Normal (n=159)	DR (n=81)
MetS (Yes), n (%)	181 (64.60)	109 (64.10)	91 (75.20)	66 (74.20)	90 (56.60)	43 (53.10)
HDL, mg/dL, $\bar{x} \pm s$	50.00±13.84	50.32±13.73	44.07±11.13	47.93±14.17*	54.62±14.02	53.05±12.75
Glu, mg/dL, $\bar{x} \pm s$	150.72±58.45	180.59±87.75***	150.86±56.11	181.90±88.18**	150.61±60.38	179.11±87.82**
SBP, mmHg, $\bar{x} \pm s$	130.99±20.42	137.04±22.97**	129.66±18.91	132.33±19.74	132.02±21.52	142.39±25.09**
DBP, mmHg, $\bar{x} \pm s$	68.65±13.44	67.96±12.31	70.71±13.09	70.50±11.39	67.10±13.53	65.18±12.74
TG, mg/dL, M(Q ₁ , Q ₃)	147.00 (100.75, 207.25)	127.00 (95.75, 192.00)	142.00 (95.50, 192.50)	132.00 (96.00, 207.00)	150.00 (108.50, 223.00)	124.00 (94.00, 178.00)*
Waist, cm, $\bar{x} \pm s$	101.96±23.17	103.01±21.06	90.06±14.08	94.69±13.78	107.56±23.28	109.94±28.39
Age, year, $\bar{x} \pm s$	63.11±10.61	63.84±10.47	62.91±10.78	62.36±10.16	63.27±10.50	65.47±10.62
CRP, mg/dL, M(Q ₁ , Q ₃)	0.32 (0.12, 0.65)	0.22 (0.13, 0.52)	0.24 (0.09, 0.56)	0.20 (0.11, 0.49)	0.35 (0.15, 0.79)	0.32 (0.17, 0.60)

Notes: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Abbreviations: DM, diabetes mellitus; DR, diabetic retinopathy; MetS, metabolic syndrome; HDL, high-density lipoprotein; Glu, fasting glucose; SBP, systemic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; CRP, C-reactive protein.

between MetS and DR.¹⁷ P -value < 0.05 was considered statistically significant.

(179.11±87.82 vs 150.61±60.38) and males (181.90±88.18 vs 150.86±56.11), all $P < 0.05$, respectively.

Results

The Baseline Characteristics of DM Patients

A total of 450 DM patients were recruited in this study, including 170 DR cases (37.80%, weighted prevalence: 34.60%) and 290 MetS participants (66.40%, weighted prevalence: 66.30%). The baseline characteristics of patients with DM are shown in Table 1. No significant differences in the MetS incidences of females and males were found between the two groups. The Glu levels in the DR group were higher than that in the non-DR group among females

Association Between MetS and DR

The proportion of the number of metabolic abnormalities is shown in Table 2 based on the severity of DR. There were 280, 111 and 59 of subjects in no retinopathy, NPR and severe NPR/PDR, respectively. Among total MetS individuals, 181 cases (62.41%) with MetS (the number of metabolic abnormalities ≥ 3) had no retinopathy, 69 (23.80%) had NPR, and 40 (13.80%) suffered from severe NPR/PDR. The results showed that no statistical differences in groups of no retinopathy, NPR and severe NPR/PDR ($\chi^2 = 3.679$, $P = 0.961$).

As shown in Table 3, the comparison for metabolic indicators based on the severity of DR was carried out. The mean

Table 2 Comparison for the Number of Metabolic Abnormalities Based on the Severity of DR

No. Abnormalities, n (%)	No Retinopathy	NPR	Severe NPR/PDR	χ^2	P
0	5 (1.80)	2 (1.80)	2 (3.40)	3.679	0.961
1	26 (9.30)	12 (10.80)	5 (8.50)		
2	68 (24.30)	28 (25.20)	12 (20.30)		
3	89 (31.80)	41 (36.90)	21 (35.60)		
4	66 (23.60)	20 (18.00)	13 (22.00)		
5	26 (9.30)	8 (7.20)	6 (10.20)		

Abbreviations: NPR, mild non-proliferative retinopathy; PDR, proliferative diabetic retinopathy.

Table 3 Association Between MetS Indicators and the Severity of DR

Indicators	No Retinopathy	NPR	Severe NPR/PDR	P
HDL	49.99±13.84	48.82±12.43	53.10±15.59	0.163
Glu	150.71±58.45	170.15±82.28	200.34±94.90	<0.001
SBP	130.98±20.42	137.32±22.68	136.50±23.74	0.017
DBP	68.65±13.44	66.37±11.27	71.05±13.69	0.079
TG	147.00 (100.75, 207.25)	125.50 (95.75, 183.50)	135.00 (93.75, 205.50)	0.371
Waist	101.96±23.17	101.83±25.46	104.17±20.79	0.311

Abbreviations: MetS, metabolic syndrome; DR, diabetic retinopathy; NPR, proliferative diabetic retinopathy; HDL, high-density lipoprotein; Glu, fasting glucose; SBP, systemic blood pressure; DBP, diastolic blood pressure; TG, triglyceride.

levels of Glu were 150.72 mg/dL, 170.15 mg/dL and 200.34 mg/dL among no retinopathy, NPR and severe NPR/PDR groups, respectively. The differences were discovered in the levels of Glu ($P<0.001$) and SBP ($P=0.017$) in the three groups.

The association between MetS and DR was assessed using Logistic regression analysis as shown in Table 4. For increasing every 1 unit in Glu among DM patients, the risk of DR development increased by 0.06 times (95% CI: 1.03–1.09, $P<0.001$). For every 1 unit increase in SBP, the risk of developing DR increased by 0.01 times (95% CI: 1.01–1.02, $P=0.004$).

The Relationship Between MetS and DR Using GAM

The results of univariate analysis showed that an EDF of 6.49 indicated a non-linear fit between Glu and DR ($P=0.001$). Similarly, an EDF of 1 suggested a linear fit

between SBP and DR ($P=0.003$). There were no differences in waist (EDF=1, $P=0.078$), TG (EDF=5.44, $P=0.083$) and HDL (EDF=1, $P=0.86$) for DR.

The results of the multivariate GAM for DR are shown in Table 5 and Figure 1, which suggested the smooth assessment for MetS in association with DR adjusted for age and gender. After controlling SBP, Glu had a linear effect on DR (EDF=1, $P<0.001$) with a positive correlation. SBP had a nonlinear influence on DR after controlling Glu (EDF=2.44, $P=0.024$).

Logistic Regression Analysis for the Risk of Vision-Related Functional Burden

The characteristics of vision-related functional burden in DM patients are shown in Table 6. A total of 150 DM cases (33.33%) suffered from the vision-related functional burden. The proportion of Q₃ difficulties in the DR group was higher than that in the non-DR group (19.40 vs 12.10, $P<0.05$). There were no statistical differences in other

Table 4 Association Between MetS and DR

Variables	OR	95% CI	P
MetS (Yes)	0.91	0.61–1.37	0.657
HDL	1.01	0.98–1.03	0.409
Glu	1.06	1.03–1.09	<0.001
SBP	1.01	1.01–1.02	0.004
DBP	0.99	0.98–1.01	0.568
TG	1.00	0.99–1.00	0.664
Waist	0.62	0.41–1.95	0.788

Abbreviations: DR, diabetic retinopathy; OR, odds ratio; CI, confidence interval; MetS, metabolic syndrome; HDL, high-density lipoprotein; Glu, fasting glucose; SBP, systemic blood pressure; DBP, diastolic blood pressure; TG, triglyceride.

Table 5 The Correlation Between MetS and DR Using GAM

Variables	EDF	PDF	Statistics	P
Univariate				
HDL	1	1	0.031	0.86
Glu	5.30	6.49	22.95	0.001
SBP	1	1	8.63	0.003
TG	4.46	5.44	9.55	0.083
Waist	1	1	3.112	0.078
Multivariate				
Glu	1.00	1.00	18.49	<0.001
SBP	2.44	3.08	9.58	0.024

Abbreviations: MetS, metabolic syndrome; DR, diabetic retinopathy; GAM, generalized additive model; EDF, effective degree of freedom; PDF, parametric degree of freedom; HDL, high-density lipoprotein; Glu, fasting glucose; SBP, systemic blood pressure; TG, triglyceride.

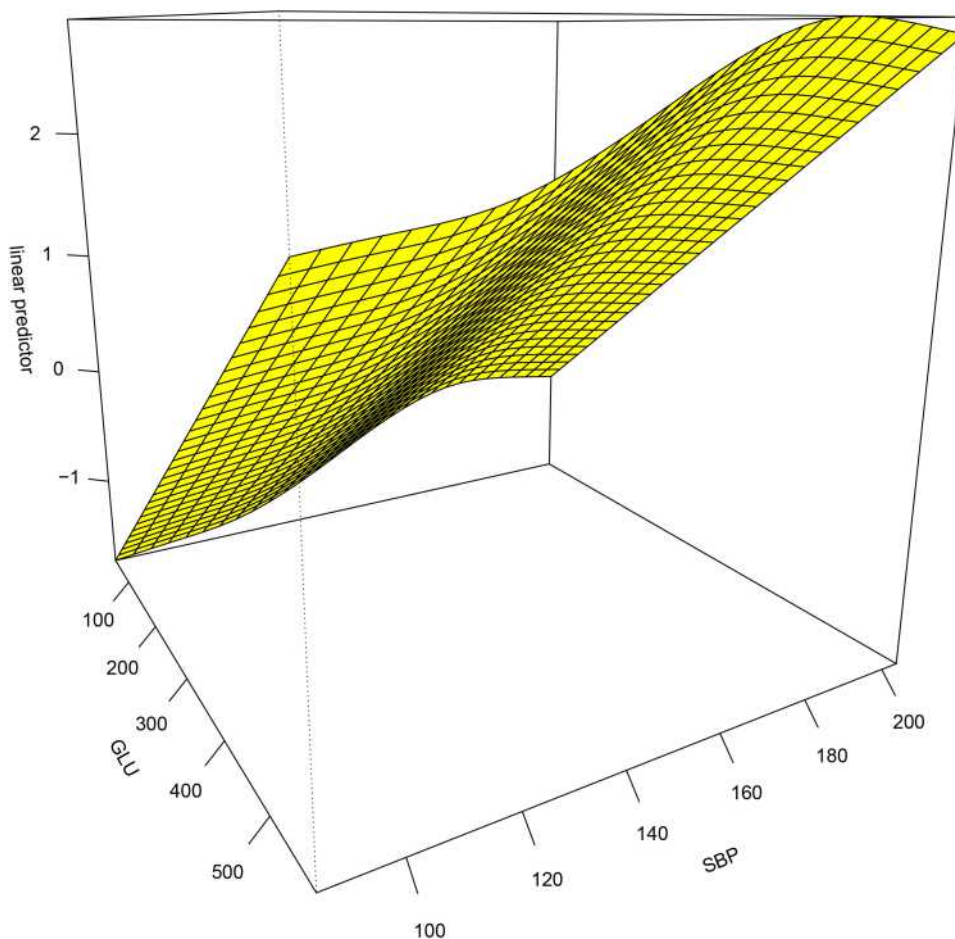


Figure 1 The GAM curve of DR.

functional difficulties of vision (Q₁, Q₂, Q₄, Q₅ and Q₆) in the two groups.

Logistic regression analysis for the risk of vision-related functional burden is displayed in Table 7. The results showed that the changes of Glu, SBP, DBP and waist were associated with the vision-related functional

burden. For increasing every 1 unit in Glu, the risk of vision-related functional burden increased by 0.007 times (95% CI: 1.004–1.011, *P*<0.001). There were 0.022-fold increase of the risk following per 1 unit increase of SBP (95% CI: 1.007–1.037, *P*=0.003). For every 1 unit increase in DBP, the risk of undergoing the vision-related

Table 6 The Characteristics of Vision-Related Functional Burden in DM Patients

Variables	Normal (n=280)	DR (n=170)	Total (n=450)
Vision-related functional burden (Yes), n (%)	88 (31.40)	62 (36.50)	150 (33.33)
Q ₁ (Yes)	42 (15.00)	33 (19.40)	75 (16.67)
Q ₂ (Yes)	34 (12.10)	20 (11.80)	54 (12.00)
Q ₃ (Yes)	34 (12.10)	33 (19.40)*	67 (14.89)
Q ₄ (Yes)	20 (7.10)	18 (10.60)	38 (8.44)
Q ₅ (Yes)	20 (7.10)	14 (8.20)	34 (7.55)
Q ₆ (Yes)	29 (10.40)	27 (15.90)	56 (12.44)

Note: **P*<0.05.

Abbreviations: DR, diabetic retinopathy; Q₁, reading; Q₂, close-up work; Q₃, looking for objects on the crowded shelves; Q₄, walking down the steps, stairs or curbs; Q₅, noticing objects to the side during ambulation; Q₆, driving.

Table 7 Logistic Regression Analysis for the Risk of Vision-Related Functional Burden

Variables	OR	95% CI	P
MetS			
HDL	1.019	0.999–1.040	0.068
Glu	1.007	1.004–1.011	<0.001
SBP	1.022	1.007–1.037	0.003
DBP	1.027	1.001–1.053	0.040
TG	1.000	0.998–1.002	0.842
Wwaist	0.935	0.888–0.984	0.010
Age	0.988	0.958–1.019	0.441
CRP	1.294	0.854–1.960	0.224

Abbreviations: MetS, metabolic syndrome; HDL, high-density lipoprotein; Glu, fasting glucose; SBP, systemic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; CRP, C-reactive protein.

functional burden rose by 0.027 times (95% CI: 1.001–1.053, $P=0.040$).

Discussion

In this present study, the association between DR and MetS in DM patients was investigated based on NHANES database. We used a GAM to assess a cross-sectional correction of DR and MetS. The findings of multivariate GAM showed that an EDF of Glu was 1, indicating a linear relation with a positive correlation of Glu and DR, and an EDF of SBP was 2.44, suggesting a nonlinear relationship of SBP and DR. We also found that a 0.06-fold and a 0.01-fold increase in the risk of DR with every 1 unit increase in Glu and SBP, respectively. It was indicated that the risk of DR may be predicted by the alternations of Glu and SBP. In addition, approximately 33.33% of DM had the vision-related functional burden. DR patients with the difficulties of looking for objects on the crowded shelves were higher than that of non-DR cases. The elevated levels of Glu, SBP and DBP were associated with the risk of vision-related functional burden.

DM, a frequent chronic hyperglycemic syndrome, affects approximately 200 million humans worldwide. It is estimated that the incidence of DM for all age-groups globally is nearly 4.4% in 2030,¹⁸ and the majority of DM patients will suffer from DR, which is a main cause of blindness in young to middle-aged adults in developed countries. It is important to pay attention to the risk factors affecting the occurrence of DR, so as to make medical strategies for reducing disease progression and preventing vision loss. MetS is a complex clinical syndrome characterized by a combination of metabolic diseases, such as obesity, hypertension, diabetes or impaired glucose regulation and

dyslipidemia. Isomaa et al reported that the prevalence of MetS in people with normal glucose tolerance, impaired fasting glucose or impaired glucose tolerance, and type 2 DM were 10%, 42%, and 78% for male and 15%, 64%, and 84% for female, respectively.¹² An early study also reported a higher incidence of DR in MetS patients, compared with non-MetS population.¹⁹ Therefore, the verified correlation between the DR and MetS needs to be identified to reduce the risk of DR.

To the best of our knowledge, prior studies reported conflicted results about the association of Glu level and DR.^{20–28} In this study, we demonstrated that a linear relationship between Glu and the risk of DR, with a positive correlation. When the normal glycolysis is blocked, glucose cannot be decomposed by a normal pathway, whereas the sorbitol pathway is activated. The aldose reductase can cause high levels of glucose to be converted to sorbitol, which is then converted to fructose by dehydrogenase. Sorbitol and fructose are rarely further metabolized in the cell, and difficultly penetrate the cell membrane due to their polarity. The osmotic pressure is increased owing to the elevated concentrations of sorbitol and fructose in the cell, which lead to the electrolyte imbalance and metabolic disorder. The selective loss of peripheral retinal capillary cells in DM patients is related to the presence of more aldose reductase in peripheral cells.²⁹ An optimized glycemic control demonstrated effective in reducing both new onset and the progression of DR.³⁰ Similarly, our findings showed that the high level of Glu was closely related to the occurrence and development of DR. In addition, we also discovered that nearly one-third of the DM cases had the vision-related functional burden. And the elevated levels of Glu was associated with the risk of vision-related functional burden. It was indicated that the blood sugar control may be effective for the risk reduction of DR and vision loss.

Hypertension, a common comorbidity of DM, has an impact in the development of atherosclerosis that can lead to the endothelial hyperplasia, sclerosis, vascular stenosis and even occlusion, then cause the retinal ischemia, hypoxia, haemangioma, and neovascularization, and eventually result in the occurrence of DR. SBP is served as a major diagnostic parameter of hypertension. A nonlinear correlation between SBP and DR was found in patients with DM in this study. UK Prospective Diabetes Study (UKPDS) reported that via regulating the blood pressure, the incidence of DR decreased by about 34% within 7 years in DM patients.³¹ Foo et al discovered that both the wide variability and the high average level of SBP were associated with moderate DR among Asian T2DM patients.³² Pang et al mentioned that the risk of DR was

increased due to the elevated blood pressure regarding SBP and DBP in objects with impaired glucose regulation.³³ These supported our results, suggesting the high level of SBP could influence the occurrence and development of DR. Moreover, elevated SBP and DBP were independent risk factors in vision-related functional burden, indicating the importance of controlling blood pressure.

Pharmacological interventions for glycemic and blood pressure control are effective for preventing or delaying the onset of DR and vision loss in those with DM. In this terrible coronavirus disease 2019 (COVID-19) pandemic moment, restrictions on timely access to medical care suggest the importance of using telemedicine. A recent study has reported the application of the telemedicine for DR screening and follow-up.³⁴ It is indicated that the importance of correct integrated management of all the figures involved in the care of DM patients (caregivers, general practitioners and different specialists) in order to avoid a different management and progression of chronic complications as observed in other diabetic microangiopathies.³⁵ The accurate program of screening and prevention, which would definitely reduce the risk of vision loss, is mandatory.

The strength of this study was the application of the GAM, of which the risk adjustment was better than other common modeling strategies for continuous covariates such as using linear regression models or categorizing linear terms.^{36,37} Our findings revealed a positive linear correlation between Glu and DR after controlling SBP, and a nonlinear correlation between SBP and DR after controlling Glu. There were several limitations that should be warranted caution for interpreting the data in this study. First, our investigation was a cross-sectional design on assessing the association between DR and MetS among patients with DM. A cross-sectional study may define a statistical correlation, but not a cause-and-effect relationship. Second, only 450 DM cases were included based on the inclusion criteria, which may reduce the statistical power. Third, data such as BMI, insulin resistance, HbA1C levels, number and severity of hypoglycemic episodes, duration and type of DM, other medications that the patient is taking, presence of ocular and other systemic co-morbidities, smoking status, alcohol use, and cognitive status were not periodically evaluated in NHANES surveys. Fourth, further detailed explanation of the relationship between dietary intake and MetS may improve the evaluation of the association between DR and MetS. Additionally, GAMs are

statistical models, in which the conventional linear relationships of multiple regression are generalized to permit a much broader class of nonlinear, but still additive relationships between response and predictor variables. A propensity to over-fit is a limitation of GAM.

Conclusion

In the current study, we conducted a cross-sectional investigation to assess the correlation of DR and MetS. Our findings showed that both Glu and SBP were associated with the occurrence of DR. There was a linear positive correlation between Glu and DR risk, and a nonlinear relationship of SBP and DR. Additionally, we also found an increased risk of vision-related functional burden when Glu, SBP or DBP levels elevated. Thus, controlling the levels of Glu and blood pressure may be beneficial in reducing the risk of DR and vision loss among the patients with DM, which may be considered as a component of telemedicine that provides the basis for early clinical intervention.

Ethics Approval and Consent to Participate

NHANES database is an open dataset in the public domain, therefore the research ethics review and the informed consent were not needed for this study.

Funding

No funding was received.

Disclosure

The authors declare that they have no competing interests.

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