Visual Functional Defects in Patients with type 2 Diabetes Mellitus: A Questionnaire Based Cross-Sectional Study

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Visual functional defects in patients with type 2 diabetes mellitus: a questionnaire based cross-sectional study

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Compliance of ethical standards

Conflict of interest

The authors declared that they have no conflict of interest

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee (Peking University Third Hospital Medical Science Research Ethics Committee, S2020023) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Abstract

Purpose

To determine the impact of type 2 diabetes mellitus (T2DM) on visual functions, identify different modifiers as risk or protective factors, and find out how these factors affect patients' visual symptoms and vision-related quality of life as a whole.

Methods

We performed an online survey among 1242 participants (400 patients, 842 non-patients).

Demographic features and severity of disease were documented, while visual functions were evaluated using National Eye Institute Visual Functioning questionnaire-25 (NEI VFQ-25). Independent t-test, analysis of variance, linear and non-linear regression models were used to assess all data.

Results

Scores other than color vision among T2DM patients were significantly lower compared with non-T2DM participants. There was significant difference after stratification of age and education, but no significant difference between different genders was observed. Parameters including duration of T2DM, fasting plasma glucose (FPG) and glycosylated hemoglobin A1c (HbA1c) negatively impacted on the scores, with 20 years' of diabetic duration, 10mmol/L of FPG, 7.5% of HbA1c being potential cut-off points. Poorer best corrected visual acuity (BCVA) and diagnosis of diabetic retinopathy were risk factors, while they simultaneously produced mediation effect, contributing 5%-78% of effect in the deterioration of visual functions caused by longer diabetic duration and higher blood glucose.

Conclusion

Significant visual impairments and faster deterioration in visual functions were seen in T2DM patients, with older age, lower educational level, longer diabetic duration, poorer blood glucose administration, limited BCVA, and the presence of diabetic retinopathy identified as risk factors. Average BCVA and diabetic retinopathy also yielded mediation effect as diabetic duration lengthened and blood glucose elevated.

Keywords

Type 2 diabetes, visual functions, retinopathy, quality of life

Introduction

Type 2 Diabetes Mellitus (T2DM) is one of the most common yet severe metabolic diseases affecting millions of people worldwide[1]. With global, regional and country-level estimates, it is predicted that the prevalence, mortality rate and health expenditure are all likely to go through a dramatic increase in both developed and developing countries[2]. Additionally, T2DM is associated with multiple ophthalmologic complications, specifically diabetic retinopathy[3] and diabetic macular edema[4], which are thought to severely impact on patients' vision and thus led to decreased vision-related quality of life and other adverse clinical outcomes. Other minor visual problems related to alterations in refractive error, contrast sensitivity, straylight and presbyopia also contributed to visual impairments and disturbance in T2DM patients. As estimated by the WHO Multinational Study of Vascular Disease in Diabetes (WMSVDD) in a 8.4-year follow-up covering 10 centers across the globe, the cumulative incidence of mild, moderate and severe visual impairments in T2DM patients were 9.43%, 3.21% and 2.25% respectively[5]. Therefore, the evaluation of visual function should serve as an importance component to assess the well-being of T2DM patients and be treated as valuable trackers or predictors that promote the overall administration of T2DM.

In prior studies, multiple rating scales featuring visual functional has already been administered to

T2DM patients with a few modifiers (e.g. old age, male gender) identified as risk factors. However, a comprehensive analysis of different influence factors of visual functions and how these factors collaboratively contribute to the progression of T2DM is still lacking. Our study aims to characterize the pattern of visual impairment among T2DM patients in comparison with individuals free of T2DM, identify certain demographic and disease-related features as protective or risk factors and analyze how they interfere with each other and promote the overall development and prognosis of T2DM.

Materials and methods

2.1 Study Design

With approval from the Ethics Committee of Peking University Third Hospital, a questionnaire was sent out to patients and volunteers via the internet. The questionnaire was divided into three parts, with the first part collecting basic information (age, gender, educational level), the second part featuring severity of disease (diabetic duration, fasting glucose, glycosylated hemoglobin A1c, best corrected visual acuity and the presence of diabetic retinopathy), and the last part determined visual performance of patients using NEI VFQ-25, which was considered as a valid tool demonstrating multiple levels of functional defects and inconvenience in conducting daily tasks among patients with chronic ophthalmologic diseases[3,6].

2.2 Study participants

In this study, questionnaires were distributed through the Internet between June 12, 2020 and August 30,

2020. A total of 1244 individuals were screened, 400 were T2DM, and 844 were non-T2DM, which yielded a representative sample for the respective communities. Further stratification was done based on patients' age and duration of T2DM. 9 groups were formed in all participants with each group possessed an age range of 10 years, while duration of T2DM were classified as 0-5 years, 5-10 years, 10-20 years, 20-30 years, and >30 years.

2.3 Information Collection

The data of basic information, diabetic-related information, vision quality and vision-related quality of life were collected. The duration of T2DM were considered as the time between initial diagnosis and the time when NEI VFQ-25 was administered to the patient, while fasting plasma glucose (FPG) and glycosylated hemoglobin A1c (HbA1c) were collected based on patients' self-reported data of recent clinical examinations. Best corrected visual acuity (BCVA) of both eyes were specified as the result from patients' last clinical visit. Decimal visual acuity, which is currently widely applied in clinical practice in China, was collected, while the data was transformed to LogMAR for analysis. Meanwhile, the presence of diabetic retinopathy was confirmed as patients having previous diagnosis in proper healthcare settings.

The scores of NEI VFQ-25 of all participants were calculated according to the following procedures. Patients were required to rate their performance in vision-related tasks with a 5 or 6 point scale ranging from "having no difficulties at all" to "not being able to do this because of eyesight". A score of 0-100 were then given to each answer as 100 being the optimum and 0 being the worst. An answer of "stop

doing this for other reasons or not interested in doing this" was considered to be missing data. The scores of 6 sub-scales were calculated as the average of scores for each question under this sub-scale, while a total score was obtained through averaging of all sub-scale scores[7].

2.3 Statistical Analysis

Statistical analysis was performed by using SPSS version 26.0 and R 4.0.4. The continuous variable and categorical variables were presented as mean±standard deviation (SD) and frequency (%), respectively. Independent t-test and analysis of variance were used to assess the data between T2DM and control group while a P-value<0.05 was considered to be significant. Moreover, we applied a non-linear regression model to describe the changes of vision-related in all sub-scales among two groups with age. We also reported the changing of NEI VFQ-25 scores induced by aging, lengthening of diabetic duration, elevation of FPG and HbA1c as well as deterioration of eyesight with restricted cubic spline (smooth curve). Further mediation effect of average vision and baseline diabetic retinopathy were assessed using mediation effect analysis.

Results

3.1 Basic data

The baseline characteristics of the participants were shown in Table 1. T2DM patients shared a mean age of 59.01±11.38 years, 11.02±8.02 years of diabetic duration, 8.16±4.00 mmol/L of FPG and 8.23±5.85% of HbA1c respectively, while a mean age of 41.64±12.76 was shared by participants

129 without T2DM. 23.7% patients with T2DM were already diagnosed with retinopathy, whereas the

130 average BCVA was 0.22±0.31 and 0.19±0.28 for the left and the right eye respectively.

131 **TABLE 1 Baseline characteristics of T2DM patients and Non-T2DM participants**

Characteristics	**T2DM (n=400)**	**Non-T2DM (n=844)**	***p*-value**
Age,years	59.01±11.38	41.64±12.76	<0.001***
Gender			
Male	188	318	<0.001***
Female	212	526	
Educational level			
Illiteracy	10	3	<0.001***
Primary School	30	6	
Secondary School	89	40	
High School	102	132	
Undergraduate	157	576	
Graduate or above	12	87	
Diabetic duration,years	11.02±8.02		
FPG, mmol/L	8.16±4.00		
HbA1c,%	8.23±5.85		
BCVA			
Left	0.22±0.31	0.15±0.18	<0.001***
Right	0.19±0.28	0.09±0.11	<0.001***

Diabetic Retinopathy	
Yes	71
No	229

n=number, T2DM=Type 2 diabete mellitus, FPG=fasting plasma glucose, BCVA=best corrected visual acuity, HbA1c= glycosylated hemoglobin A1c

$p<0.001$ was marked with ***.

3.2 Functional defects in T2DM patients and Non-T2DM participants

Both groups completed the questionnaire and visual functional defects in all participants were relatively slight since mean scores for most sub-scales exceeded 90, demonstrating satisfactory performance in all participants. Notably, the scores for "General Vision", which was based on the personal assessment of vision-related quality of life, were comparably lower in both groups, indicating the need of alleviating visual symptoms or bettering visual performance even in participants not suffering from T2DM.

As shown in Table 2, the total and mean scores for 5 NEI VFQ-25 sub-scales scores were lower in T2DM group ($p<0.001$, independent t-test). However, there was no significant difference between the two groups in the scores of color vision. Furthermore, after stratification by age, gender and educational level, we found that the performance of elderly patients with T2DM were worse than those non-T2DM participants of the same age, in terms of distance activities ($p=0.033$), social functioning ($p=0.006$), peripheral vision ($p=0.025$) and total score ($p=0.013$) (Supplementary Table 1). Similar

stratification was done with regard to gender and educational level. These results indicated that all sub-scales and total score in T2DM patients were lower than non-T2DM participants except for color vision after stratification by gender (Supplementary Table 2), while significant results were only seen in participants sharing an educational level of secondary school, high school and undergraduate (Supplementary Table 3). The scores of near activities (p=0.007) and distance activities (p=0.021) of T2DM with secondary school education background were lower than non-T2DM counterparts. Undergraduate T2DM patients, however, reported greater functional defects in near activities and social functioning with statistical significance (p<0.001, p=0.012) compared with non-T2DM participants.

TABLE 2 Visual functional defects among T2DM patients and non-T2DM participants

Parameters	**T2DM (n=400)**	**Non-T2DM (n=842)**	***p*-value**
Near activities	82.46±21.90	92.63±12.09	<0.001***
Distance activities	87.69±19.25	92.22±11.60	<0.001***
Social functioning	93.25±15.17	97.17±8.19	<0.001***
General vision	64.35±15.38	68.15±15.77	<0.001***
Peripheral vision	90.87±19.38	94.93±12.19	<0.001***
Color vision	94.68±15.28	93.98±13.47	0.423
NEI VFQ-25 Total	89.55±16.11	94.18±8.61	<0.001***

n=number, T2DM=Type 2 diabete mellitus, NEI VFQ-25=National Eye Institute Visual Functioning questionnaire-25

p<0.001 was marked with ***.

Furthermore, we applied a non-linear regression model to analyze the changes of vision-related subscales with age. As shown in Figure 1, near activities in both T2DM and non-T2DM participants presented constant decrease with age, whereas in other sub-scales, two groups were expected to reach their highest functional level at around age 40-50. Moreover, in sub-scales with such single peak shaped pattern, peak performance for T2DM patients seemed to be relatively lower than non-T2DM participants, while the scope of functional loss was higher after age 60. In the general vision sub-scale, non-T2DM participants tended to demonstrate a different pattern compared with T2DM patients as there was no direct negative correlation between the average score and age. Color vision, however, didn't exhibit a clear pattern of functional loss, as the mean score for this sub-scale didn't differ much as T2DM patients got older. These results indicated that apart from the lower scores in each sub-scale, T2DM patients simultaneously experienced faster worsening of various visual functions as they senesced.

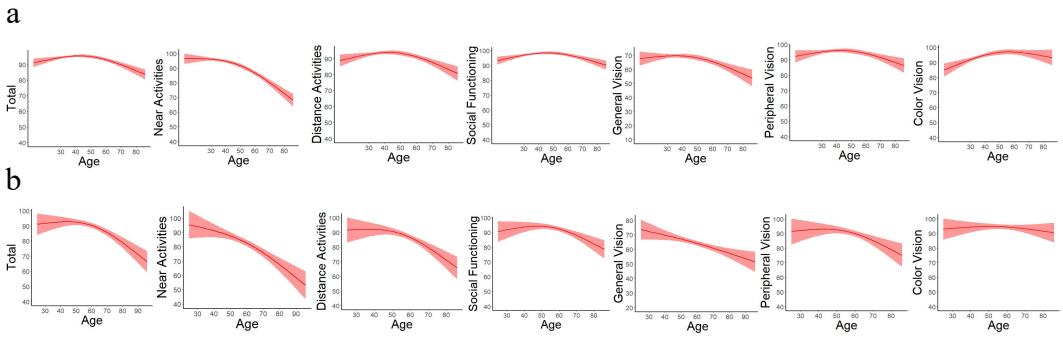

FIGURE 1 Correlation between visual functions and aging in T2DM patients (a) and non-T2DM participants (b). We used restricted cubic spline to characterize the non-linear correlation between aging and scores for each sub-scale in NEI VFQ-25, 95%CI were shown with the lighter red ribbon around the smooth curves.

3.3 Influence factors of visual loss in T2DM patients

3.3.1 Demographic variables in T2DM patients

When demographic variables of T2DM patients, including age, gender and educational level were examined independently, we found that all these modifiers contributed to the overall effect of the hyperglycemic metabolic disorder (Table 3). In all sub-scales other than color vision, older age and lower educational level contributed to lower scores of NEI VFQ-25, therefore indicating higher risks of visual functional loss and heavier dependence on caregivers in vision-related tasks. Female patients exhibited poorer visual performance, however, we found that gender had no effect on the decline of visual function after matching female and male patients with age. Among all demographic features, the age of patients had the greatest impact on visual impairment, as the *F*-value for age, gender and education level were 6.592, 3.026, and 1.068, respectively. In the color vision sub-scale, on the contrary, none of all the demographic features were shown to leave either positive of negative effect.

TABLE 3 Visual functions in T2DM patients stratified by demographic features

Subscales	Near Activities	Distance Activities	Social Functioning	General Vision	Peripheral Vision	Color Vision	Total
Age							
20-29	95.83	91.67	93.75	70.00	87.50	100.00±	93.75±8
(n=2)	±5.89	±11.79	±8.84	±14.14	±17.68	0.00	.84
30-39	92.95	93.27	95.67	72.31	92.31	96.00	93.93
(n=26)	±15.58	±12.25	±11.15	±15.05	±13.73	±11.81	±11.44

40-49	90.85	93.44	93.88	68.09	95.21	93.18	93.38
(n=47)	±16.14	±15.14	±11.15	±16.50	±14.41	±20.43	±15.04
50-59	84.46	90.09	95.16	64.86	92.79	95.27	91.55
(n=111)	±18.00	±15.06	±13.18	±14.82	±16.30	±12.84	±12.83
60-69	81.97	88.92	94.84	63.89	92.48	95.60	90.74
(n=144)	±22.39	±17.94	±12.35	±15.20	±19.01	±14.37	±14.51
70-79	71.53	75.68	87.09	59.34	81.25	91.67	81.35
(n=61)	±26.05	±24.62	±18.95	±14.59	±24.63	±18.79	±18.69
80-89	67.86	70.23	71.43	57.14	78.57	95.00	73.78
(n=7)	±28.23	±43.53	±31.22	±13.80	±39.33	±11.18	±33.86
90-99 (n=1)	12.5	-	-	40	-	-	12.5
***p*-value**	<0.001***	<0.001***	<0.001***	0.004**	0.001**	0.699	<0.001***
Gender							
Male	86.25	91.01	94.65	67.02	93.05	95.30	91.98
(n=188)	±18.11	±16.49	±12.49	±15.54	±16.75	±14.63	±13.46
Female	79.11	84.74	92.00	61.98	88.93	94.14	87.40
(n=212)	±24.34	±21.01	±17.14	±14.89	±21.31	±15.84	±17.89
***p*-value**	0.001**	0.001**	0.077	0.001**	0.032*	0.451	0.004**
Educational level							

Illiteracy (n=10)	54.17 ±32.45	66.67 ±26.06	83.75 ±16.72	50.00 ±23.57	62.50 ±29.46	86.11 ±18.16	70.13 ±19.57
Primary School (n=30)	70.09 ±28.76	78.89 ±24.34	87.5 ±24.34	60.67 ±16.17	84.17 ±24.99	90.18 ±24.85	82.27 ±22.47
Secondary School (n=87)	79.07 ±23.47	86.84 ±18.82	93.47 ±12.57	62.25 ±16.08	92.82 ±16.13	94.54 ±13.44	88.58 ±16.69
High School (n=106)	82.39 ±21.48	88.19 ±19.66	92.89 ±15.98	64.12 ±14.44	90.67 ±20.19	95.05 ±14.15	89.85 ±15.91
Undergraduate (n=152)	87.85 ±16.65	90.39 ±17.00	94.63 ±13.77	66.62 ±14.03	92.63 ±17.56	95.75 ±14.84	92.13 ±13.38
Graduate or above (n=12)	90.28 ±12.73	93.75 ±8.79	98.96 ±3.61	73.33 ±15.57	95.83 ±9.73	95.83 ±9.73	94.93 ±7.00
***p*-value**	<0.001***	<0.001***	0.045*	0.001**	<0.001***	0.293	<0.001**

n=number

p<0.05 was marked with* *p*<0.01 was marked with** *p*<0.001 was marked with***

3.3.2 Diabetic parameters in T2DM patients

Moreover, we evaluated the duration of T2DM, FPG and HbA1c level, which were key factors determining the degree of T2DM to explore their impact on the vision function related to quality of life. As shown in Figure 2A, the duration of T2DM negatively correlated with scores of each sub-scale and total score of NEI VFQ-25 except for color vision. The scores of patients with a course of more than 20 years decreased significantly, suggesting that 20 year is a significant cut-off point. With the extension of the course of diabetes, the scores of near activities decreased gradually and might serve as a more sensitive parameter in evaluating visual loss.

Elevated fasting blood glucose affects near activities, distance activities, social functioning, color vision and total score (Figure 2B). In peripheral version sub-scale however, significant functional loss wasn't observed until patients' FPG reached 10mmol/l, whereas scores for general vision didn't differ much when patients' FPG exceeded 15mmol/l, as relative lower FPG level and better control of T2DM's hyperglycemic effect might elevate patients' expectation in vision-related quality of life and lower their general satisfaction regarding visual functions.

As an indicator of blood glucose control in recent 3 months, HbA1c will also affect visual function. With the increase of HbA1c, all sub-scales and the scores of NEI VFQ-25 decreased gradually. Total as well as mean score for near activities and peripheral vision decreased with the increase of HbA1c, while scores for social functioning went through a cut-off point as the scope of decrease changed when HbA1c reached around 7.5%. Additional multivariate analysis indicated that diabetic duration, FPG

and HbA1c level had influence on scores of NEI VFQ-25. However, duration of T2DM produced the highest proportion of overall visual impairments among the three, with a *F*-value of 1.842 compared with FPG (*F*=1.344, multivariate analysis) and HbA1c (*F*=1.069).

3.3.3 Ocular parameters in T2DM patients

Moreover, the correlation between the average BCVA of both eyes, the presence of retinopathy and visual functional loss were examined using both non-linear regression model and independent t-test. As shown in Figure 2D, scores for each sub-scale and total score were found to decrease as BCVA worsened, with potential cut-off point identified at an average BCVA of 0.4. Color vision, however, weren't shown to display either positive or negative correlation with average BCVA of both eyes. The presence of diabetic retinopathy (DR), which was the main symbol for micro-vessel degeneration caused by chronic hyperglycemic condition, did present statistically significant results. DR sufferers, however, exhibited poorer performance in all sub-scales and total scores of NEI VFQ-25, with a *p*-value of 0.013 in color vision and $p<0.001$ in all other sub-scales, respectively.

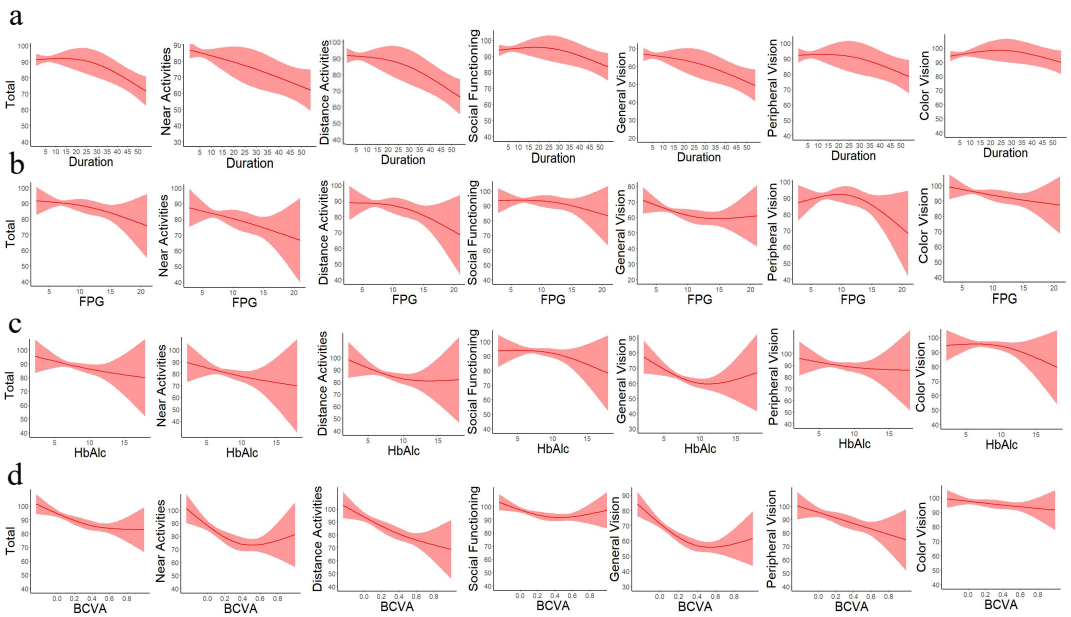

FIGURE 2 Correlation between visual functions and diabetic duration (a), FPG (b) , HbA1c (c) and average vision (d) Smooth curves along with 95%CI were demonstrated above indicating the progression of functional loss in each vision-related sub-scales as duration of T2DM lengthened, FPG and HbA1c elevated and average vision deteriorated.

In general, older age, lower educational, long duration of T2DM, elevated FPG and HbA1c level were identified risk factors involved in visual impairment, whereas age and duration of T2DM were the two most important factors. Poorer BCVA and the presence of diabetic retinopathy, on the other hand, were not only independent risk factors, but also essential mediators in the long-term effect of longer duration of T2DM, higher FPG and HbA1c level.

3.3.4 Mediation effect analysis of different modifiers

Through analysis of relationship between diabetic duration, BCVA and scores for sub-scales as well as total scores of NEI VFQ-25, we found that longer duration negatively impacted on T2DM patients' multiple visual functions through deterioration of average BCVA, and mean proportion of the mediation effect in different sub-scales ranged from 19.20% to 42.70%. Similar mediation effect was found in FPG, HbA1c and NEI VFQ-25. The proportion of mediation effect was shown in Table 4, which pointed out that the mediation effect of average BCVA was more statistically significant than the presence of diabetic retinopathy Furthermore, color vision and social functioning sub-scale were the least likely to be influenced by the mediation effect of the two ophthalmologic parameters. General vision on the contrary, was demonstrated to have BCVA and the presence of retinopathy share the

largest proportion of contribution, as subjective thoughts towards one's general vision might be the most sensitive to subtle changes in eyesight and was the earliest sub-scale to be influenced by the diagnosis of diabetic retinopathy.

TABLE 4 Mediation effect of BCVA and diabetic retinopathy

Mediation Effect (%)	Near Activities	Distance Activities	Social Functioning	General Vision	Peripheral Vision	Color Vision	Total Score
Diabetic duration-BCVA	19.93***	28.06***	19.20*	36.40**	42.70**	20.89	29.22***
FPG-BCVA	47.30***	46.60***	51.70***	58.20***	54.50***	25.40**	62.00*
HbA1c-BCVA	29.60*	55.81**	5.56	18.20*	27.40*	1.97	27.89
Diabetic duration-Retinopathy	77.6	49.01	63.42	33.00	61.57	52.91	73.77
FPG-Retinopathy	33.40	21.70	18.90	29.70	24.10	8.97	24.80
HbA1c-Retinopathy	19.20	11.90	13.69	60.20	5.97	5.79	15.50

FPG=Fasting plasma glucose, HbA1c=glycosylated hemoglobin A1c, BCVA=best corrected visual

acuity

$p<0.05$ was marked with* $p<0.01$ was marked with** $p<0.001$ was marked with***

Discussion

Our study presented a cross sectional survey that examined visual functional loss in T2DM patients, identified risk factors as well as protective factors that modified patients' performance. We found that visual functional loss was more common and significant in T2DM patients compared with non-T2DM participants, with the scope of visual impairment in T2DM patients shown to be larger and the progression comparably faster. Old age, low educational, long duration of T2DM, elevated blood glucose level (FPG and HbA1c), poor BCVA and the presence of diabetic retinopathy negatively correlates with visual performance and vision-related quality of life among T2DM patients. 60 years of age , 20 years of diabetic duration, 10 mmol/L of FPG, and 7.5% of HbA1c might be the cut-off point of vision decline. Average vision and the presence of retinopathy, on the other hand, were either independent modifiers and essential mediators that mediated the effect of diabetic duration, FPG and HbA1c level.

In our study, the degree of visual loss was found to be of a higher extent in T2DM patients than non-T2DM participants, while the visual functions of T2DM patients decreased more significantly as age increased. As reported in prior studies, older patients were more susceptible to stressors contributing to diabetic vascular changes, including oxidative stress, metabolic products and other toxic transmitters[3,8,9]. Patients of older age also suffer from more complicated comorbidities and geriatric syndromes, which brought challenges to proper glycemic control and thus were likely to go through

rapid impairments of functional loss in vision-related activities[10].

Applying a non-linear regression model, we identified that both T2DM patients and non-T2DM participants exhibited a single-peak shaped pattern of functional loss as age grew. Younger patients, however, weren't shown to perform better than patients in their 40s or 50s. For T2DM patients, on the one hand, this single peak-shaped correlation might be explained with the fact that those who developed T2DM at younger age probably suffer from more severe eye disease and yet were more sensitive to functional loss in vision-related activities. As reported by Song et al[11], the prevalence and degree of visual loss in T2DM increased substantially after patients reached their middle age, while studies featuring younger population indicated that diabetic retinopathy in prepubescent children, teenagers and young adults might be of higher severity and faster progression since insulin requirements in adolescence were relatively high, and teenage hormonal axis were immature and less sensitive to drugs[12]. On the other hand, younger non-T2DM patients might generally go through more frequent yet complicated visual tasks and required higher vision related quality of life compared with senior participants, which helps to explain why young participants scored lower than middle-aged participants. In the general vision sub-scale however, there was no significant differences in scores between two groups, which could possibly be explained by the fact that non-T2DM participants were more involved in vision-related tasks and thus set a higher standard for maintaining satisfactory visual performance. We concluded that both adolescent and senior T2DM patients should be paid with special attention as their physical condition featured more complicated comorbidities, higher hormone requirements and lower compliance, which therefore called for strict glycemic control and systematic disease administration.

Paralleled to prior studies, both old age and low educational level were thought to be risk factors predicting poorer visual functions and vision-related quality of life[2,13,14]. Effect of other demographic features such as gender varied in different cohorts. In 2013, a study in Japan found that female participants had a higher prevalence of diabetic retinopathy at baseline and were more likely to develop severe retinopathy with the development of diabetes[15]. However, more studies suggested that the male sex was an independent risk factor for the high prevalence and progression, emphasizing the protective effect of estrogen and identifying testosterone and androgen as detrimental to diabetic micro-vascular complications[16,17].

For parameters determining severity of T2DM, duration of disease, elevated FPG and HbA1c level were generally found to negatively impacted on visual performances. Nonetheless, different edge points were confirmed in different studies. Olivarius et al used a FPG 10 and 17 mmol/L along with a HbA1c 9% and 11% respectively, whereas Foo et al ascertained a transformation zone of HbAlc 7%-8%[14,18]. The variation in the selection of the cut-off point for HbA1c could be explained by the different study procedures in two cohorts. Olivarius et al on the one hand, used average vision as the major parameter assessing visual loss, while on the other hand, moderate diabetic retinopathy was seen as the observational outcome in the latter report[14]. Moderate diabetic retinopathy, diagnosed by proliferation of micro-vessels through fundus photography, led to a lower cut-off point of HbAlc, with subjective visual loss being less sensitive and were unable to give an early warning of visual loss until HbAlc reached 9%[14,18]. Therefore, we suggested that fundus degeneration symbolized by vascular changes, which was sensitive to hyperglycemic conditions, might accounted for the low scores in relative sub-scales as diabetic duration lengthened and blood glucose level elevated. Moreover, 20

years' of diabetic duration were regarded as probable cut-off point in a Tunisian cohort conducted in 2014[19], while Liu et al reported 15 years to be a meaningful stage symbolizing severe ocular degeneration[20]. Such differences were possibly due to the different definitions of visual loss, as outcome indicators were subjective visual symptoms in some studies while others used rating scales or ocular examinations as diagnostic tools. In our study, both subjective evaluation of visual loss and objective tools determining BCVA were applied, with more detailed definition of different types of visual functional defect and degree of decreased vision-related quality of life using the NEI VFQ-25 rating scale. Such combination of diagnostic tools defined relatively sensitive cut-off point of HbAlc and FPG level, while the cut-off point of T2DM duration were not as sensitive as expected. This emphasized the need for appropriate yet comprehensive combination of different diagnostic tools, and also early intervention of T2DM as no golden standard of cut-off points were so far established. Additionally, the insignificant effect of early elevation of FPG and HbAlc were possibly due to the fluctuation of long term glycemic control, as related studies stated that the oscillation of blood glucose boasted higher predictive value rather than parameters determining average blood glucose level[21,22].

Ocular parameters, namely average BCVA and baseline retinopathy in our study, were considered as essential modifiers of visual functions. Poorer vision and the existence of ocular vascular degeneration limited the scale and acuity of optesthesia in T2DM patients thus disturbed their vision-related quality of life in several ways including elevating intraocular pressure and damaging nerve fiber layers[19,23]. However, some reports revealed the protective effect of myopia on the development of diabetic retinopathy, which may indicate that patients suffered from myopia were less likely to develop diabetic retinopathy, but such protective effect disappeared once diabetic retinopathy ensued.

The mediation effect of average BCVA and baseline diabetic retinopathy, accounted for different proportions of functional loss in various NEI VFQ-25 sub-scales. General vision was the most sensitive sub-scale influenced by poor eyesight, as participants mainly judge their autonomous performance in vision-related daily tasks based on the average vision of both eyes. The different proportion of mediation effect generated by average BCVA and baseline diabetic retinopathy helped to illustrate that early degradation of eyesight or diagnosis of retinopathy were relatively asymptomatic, as they might not be directly reflected by clear signs of vision-related disabilities in daily life. Furthermore, visual symptoms other than decreased eyesight and ophthalmologic diagnosis besides diabetic retinopathy were equally important and needed to be carefully taken into consideration.

Another interesting finding regarding visual loss was the patients' performance in color vision. As mentioned previously, the decline in color vision, which was embodied by the ability to choose clothes in NEI VFQ-25, was not associated with the development of T2DM. Moreover, little evidence of either positive or negative correlations found between several modifiers and color vision scores. Such insignificant results contradicted with prior studies reporting loss of color vision in T2DM patients and associating risk factors with deteriorated color vision[24,25]. Yet the contradictory findings might be due to the fact that the setting of evaluating loss of color vision were different. Some cohorts came up with the conclusion using specific rating scales such as D-15 color test or Cambridge color test while others were based on integrated rating scales assessing general vision-related quality of life. Still other methods such as machinery tests or patients' subjective feedback were included in some studies. However, it was still worth noticing that most color vision loss were sub-clinical and might not be

detected using certain techniques. Additionally, the subtle loss of color vision could be covered by physiological decline in color vision caused by aging, therefore called for early evaluation of color vision and visual complications accompanying T2DM.

Above all, the confirmation of effect driven by different modifiers and the pattern of functional loss in T2DM patients collaboratively promoted the urgent need of early diagnosis, in-time intervention, strict administration and systematic follow-up of all T2DM patients. T2DM patients with multiple risk factors should be paid with more attention and patient-centered therapeutic strategies should be administered. Efficient screening and timely treatment using portable eye examination units guaranteed decreased rate of visual impairments by 86% in T2DM patients, as reported by a Finnish cohort carried out in more than 14 thousand patients, emphasizing valuable prospective value of taking early action by healthcare professionals[26]. Moreover, the absence of intensive blood glucose administration may exacerbate the progression of T2DM. Hu et al reported thatpositive correlation between annual increase of FPG and narrowing of retinal arterioles[27].

There are several limitations to our study. First, it is a cross-sectional study via an online questionnaire, through which a strict causal relationship or quantified correlations between each modifier and functional loss cannot be concluded. Second, quality control was based on the time that each participant spent completing the questionnaire only, which might not be sufficient to prevent certain recall bias. Third, we didn’t specifically match every T2DM patient with a non-T2DM participants whose basic information were similar, instead, rough classification of all participants was done according to a 10-year age range. Therefore, longitudinal data from larger samples was needed to verify

the above conclusions, and further research might investigate the mechanism and progression of certain ophthalomogic complications and find out certain parameters with predictive values.

To sum up, our study suggested that attention should be paid to the visual function of patients with T2DM , specifically in patients with old age, low educational level, long course of disease, irregular self-monitoring of blood glucose, limited eyesight, and those who had already been diagnosed with diabetic retinopathy. Certain cut-off points were identified, whereas ophthalomogic parameters served as essential mediators of the overall long-term hyperglycemic effect. We emphasized the importance of early diagnosis, in-time intervention and careful administration of T2DM and use more comprehensive parameters to evaluate the severity of visual functiong in T2DM patients.

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