Article Title: Evaluation of Vision Related Quality of Life in Turkish Patients with Diabetic Retinopathy

Diyabetik Retinopatisi olan Türk Hastalarda Görmeyle İlişkili Yaşam Kalitesinin Değerlendirilmesi

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ABSTRACT

Purpose: Diabetic retinopathy (DR) is one of the major causes of vision loss and blindness in adults. DR was associated with qualitative and quantitative losses in vision related quality of life (VRQOL). Determination of VRQOL and evaluation of some blood parameters might be related to visual functioning questionnaire (VFQ) scores in patients with DR. The aim of the study is to determine VRQOL in patients with and without DR.

Materials and Methods: A case- control study has been performed in case and control groups. Nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) cases were matched to patients with diabetes mellitus (DM) and without diabetic retinopathy (DR) in terms of age, sex, and duration of DM in the head-to-head study. A Turkish version of National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) including 25 items was conducted.

Results: Mean duration of diabetes was 136.34±100.6 months. 29.6% of the patients had mild NPDR, 29.6% had moderate-severe NPDR and 40.8% had PDR. 33 patients had macular edema (ME). In this group, 60.6% had severe NPDR and 39.4% had PDR ($p<0.001$). VFQ-25 scores were found higher in control group ($p<0.001$). PDR and macular edema (ME) were the most important parameters that effect VRQOL in logistic regression analysis.

Conclusion: It was shown that VFQ-25 was impaired in patients with PDR and ME. We believe that, the patients who have chronic diseases like PDR should be regularly examined in order to increase the quality of life and improve the prognosis.

Key Words: Vision related quality of life, BUN, diabetic retinopathy, diabetes mellitus, HbA1c.

ÖZ

Amaç: Diyabetik retinopati (DR), erişkinlerde görme kaybı ve körlüğün önde gelen sebeplerinden biridir. DR, görmeyle ilişkili yaşam kalitesinde (GİYK) kalitatif ve kantitatif kayıp ile ilişkilidir. DR'li hastaların GİYK ve bazı kan değerlerinin değerlendirilmesi görme fonksiyonu skoruna etki edebilir. Bu çalışmanın amacı DR'si olan ve olmayan hastalarda GİYK skorlarının değerlendirilmesidir.

Gereç ve Yöntemler: Nonproliferatif DR (NPDR) ve proliferatif DR (PDR) olguları, retinopatisi olmayan diabetes mellitus (DM) hastaları ile yaş, cinsiyet ve diyabet süresine göre bire bir olarak eşleştirilmiştir. Yaşam kalitesi değerlendirmesinde National Eye Institute Visual Function Questionnaire (NEI-VFQ-25)'in Türkçe versiyonu kullanılmıştır. Araştırmada 200 DM hastasının rutin oftalmolojik muayenesi yapılmış, açlık kan şekeri, hemoglobin A1c (HbA1c), kan üre nitojeni (BUN) ve kreatinin düzeyleri ölçülmüştür.

Bulgular: Çalışmada hastaların ortalama DM süresi 136.34±100.6 aydır. Olguların %29,6'sında hafif NPDR, %29,6'sında orta-ileri NPDR ve %40,8'inde PDR; 33'ünde maküler ödem (MÖ) saptanmıştır. MÖ olan hastaların, %60,6'sında ileri NPDR ve %39,4'ünde PDR saptanmıştır ($p<0.001$). VFQ-25 ölçeği skorları retinopatisi olmayan DM hastalarında daha yüksek saptanmıştır ($p<0.001$). Lojistik regresyon analizinde PDR ve MÖ'nün GİYK'yi etkileyen en önemli değişkenler olduğu görülmüştür.

Sonuç: MÖ ve PDR olan hastalarda VFQ-25 skorlarının düştüğü saptanmıştır. GİYK'yi artırmak ve prognozu iyileştirmek amacıyla PDR gibi kronik hastalıklar yakın gözlem altında tutulmalıdır.

Anahtar Kelimeler: Görmeyle ilişkili yaşam kalitesi, BUN, diyabetik retinopati, diyabetes mellitus, HbA1c

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1. INTRODUCTION

Diabetic retinopathy (DR) is one of the major causes of vision loss and blindness in adults and it is related to microvascular complications of diabetes mellitus (DM).[1] DR develops approximately in two decades after DM was diagnosed.[2] DM prevalence is higher in developing countries. This can be attributed to industrialisation and westernised lifestyle together with aging. DM and DM related complications are major public health problems in Turkey. Most of the patients have type 2 DM and the prevalence of DM was 13.7% on 2003 and 16.5% on 2009 in Turkish adult patients.[3,4]

DR was associated with qualitative and quantitative losses in vision related quality of life (VRQOL), as mentioned in numerous articles.[5-9] DR development is highly related to the duration of type 2 DM. The risk of DR increases to 90% in ten and more years.[2] The increased levels of blood urea nitrogen (BUN) and creatinin are strongly associated with proteinuria which is a precursor of retinopathy.[10] Glycated hemoglobin (HbA1C) and fasting plasma glucose levels (FPG) are used in diagnoses of DM as recommended by American Diabetes Association.

The impact of DM and complications on vision quality are well known. DR and visual function has been evaluated in several studies by using different instruments to measure health related quality of life (HRQOL), on the other hand, VRQOL scale has been used rarely.[5-9]

Evaluation of the impact of DR on vision related health quality and the factors associated to visual function are crucial for the management of DM patients in clinical practices. Therefore we aimed to measure VRQOL score of DR patients and to explore the risk factors that effect VRQOL in a comparative study.

2. MATERIALS AND METHODS

2.1. The study population

This study was conducted at the eye clinic of one of the referral hospitals in Ankara. The hospital has five different eye departments and approximately 500 patients are examined daily. The sample design and sample size was calculated by using DR prevalence, 0.80 power and 95% CI.

Patients were recruited to study from ophthalmolgy clinics between May 1 and July 31, 2015. Patients that were diagnosed and monitored in endocrinology clinics and accepted to participate were taken on for advanced examinations. The study was compromised outpatients with nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) and controls with similar sociodemographic features. Patients in control group had simple refractive errors and DM without DR. The study was performed with 98 DR cases and 102 diabetic controls.

2.2. Definiton of DM

DM was either defined as fasting glucose level >126 mg/dL or HbA1c levels higher than 6.5%. Patients with documantated history of DM or patients using anti-diabetic agents were accepted as diabetic and recruited to study.

2.3. Definition and Grading of DR

DR was defined as retinopathy with definite diabetes mellitus. Grading was made according to the American Academy of Ophthalmology (AAO) International Clinical Diabetic Retinopathy Disease Severity Scale[11] with indirect ophthalmoscopy as follows; mild NPDR; moderate NPDR; severe NPDR; or PDR. Clinically, significant diabetic macular edema (ME) was defined according to Early Treatment Diabetic Retinopathy Study (ETDRS). The degree of DR was categorized based on the worse-seeing eye.

2.4. Exclusion criteria

Patients that had refraction errors ± 2 diopters, <23 mm and >25 mm of axial length, glaucoma, uveitis, eye trauma, vitreoretinal manipulations like panretinal or grid laser, intravitreal enjections or vitreoretinal surgery were excluded from the study in order to see the natural progress of the disease.

2.5. Ethics

All participants provided informed consent. This study design followed the participants of the Declaration of Helsinki for biomedical research and was approved by the Institutional Review Board of the Dışkapı Yıldırım Beyazıt Education and Research Hospital (03.11.2014 - 17/09).

2.6. Data collection

Data collection was composed of three parts: Standard questionnaire, patient folder data and ophthalmologic examination.

Information regarding demographic and social factors was obtained by using a standardized 32-item questionnaire during a health interview. Vision related health quality was also identified in the same interview by using Turkish version of National Eye Institute Visual Function Questionnaire (NEI-VFQ-25).[12] The NEI-VFQ-25 is a vision-specific questionnaire that has been used to assess the visual impairment in age-related macular degeneration[13], glaucoma[14], blepharospasm[15], diabetic eye disease[16], retinitis pigmentosa[17] and dry eye syndrome[18]. It is composed of 12 subscales: general health (1 item), general vision (1 item), ocular pain (2 items), near activities (3 items), distance activities (3 items), vision-specific social functioning (2 items), vision-specific mental health (4 items), vision-specific role difficulties (2 items), vision-specific dependency (3

items), driving (3 items), color vision (1 item) and peripheral vision (1 item).[19]

Vision specific score was calculated by using vision specific subscales. The 3 subscales were combined and a new variable that can substitute visual capacity was formed. The overall vision-specific function score was divided into tertiles representing low, moderate and high vision-functioning levels.[20] Logistic regression analysis was used to compare high visual functionality (reference) with low visual functionality.

Various VFQ associated factors were examined. In participants with a history of DM, random blood glucose levels, fasting blood glucose levels, HbA1C levels, BUN and creatinin levels were recorded from their patient folders from last visits to their endocrinology clinics. Fasting glucose, HbA1c were measured at a certified central laboratory.

2.7. Statistical Analyses

The VFQ scores of DR patients were assessed with 95% confidence intervals (CI). ANOVA and the chi-square tests were used to compare the demographic characteristics. The duration of DM was calculated as the difference between the year of diagnosis and the examination year.

To compare the DR levels, some continuous variables were transformed into categoric variables, and linear regression analysis was performed to evaluate the potential variables related to VFQ score. Dummy variables formed for categorical variables in order to put in regression model. Comorbidity and macular edema (ME) was used as yes (0) and no (1), DR was normal to PDR (0-3) and DM duration, FBG, HbA1C levels, BUN and creatinin levels were used as continuous.

Analyses were performed by using the Statistical Package for the Social Sciences ver. 20.0 (SPSS, Inc.,Chicago, IL).

3. RESULTS

200 individuals have completed the NEI-VFQ-25 questionnaires and they were included in the study. 102 individuals were randomised (or splitted or recruited) to control group and 98 patients were randomised to study group. 15% of the individuals were still working, 16.5% were in high school and overeducated and 83% had middle income level. 44% had chronic diseases other than DM and 95% were using antidiabetics. 58 of the patients were NPDR (50% mild, 50% moderate-severe), 40 of them were PDR. There were no statistically significant differences at gender, marital status, employment, monthly income and education between the study and control groups (p>0.05).

Mean age at control group was 62.59(±9.6). Mean ages at mild NPDR, moderate-severe NPDR and PDR groups were 62.41(±9.9), 62.72(±7.9) and 63.65(±10.9) respectively (p=0.071). Co-morbidities accompanying DM were hypertension, hypercholesterolemia, renal disease and cardiac disease. The co-morbidity rates were 32.4% at control group and 48.3% at mild NPDR (p=0.560). Best corrected visual acuity at right and left eye was 0.95(±0.1), 0.96 (±0.1) in control group and 0.29(±0.2) and 0.35(±0.1) in PDR group respectively (p<0.001). 33 participants had macular edema (ME). In this group, 60.6% had severe NPDR and 39.4% had PDR (p<0.001) (Table 1).

Mean HbA1c levels were 7.612%(±1.9), 7.921%(±1.6), 8.931%(±2.0) and 8.148%(±1.7) (p=0.009); mean BUN levels were 34.97(±13.2) mg/dl, 32.03(±10.8) mg/dl, 50.64(±42.1) mg/dl, 41.83(±16.1) mg/dl (p=0.001); mean

Table 1. *Socio-demographic characteristics of study groups (N=200)*

Variables*	Controls	Mild NPDR	Severe NPDR	PDR	p-value
Age	62.59 (9.6)	62.41 (9.9)	62.72 (7.9)	63.65 (10.9)	0.071
Marital status: Married	89 (87.3)	25 (86.2)	26 (89.7)	34 (83.3)	0.897
Co-morbidities: Present	33 (32.4)	14 (48.3)	18 (62.1)	19 (47.5)	0.560
Gender: Female	71 (69.6)	15 (51.7)	19 (65.5)	25 (62.5)	0.350
Unemployed	51 (50.0)	14 (48.3)	16 (55.2)	18 (45.0)	0.699
Income: Low	7 (6.9)	3 (10.3)	1 (3.4)	2 (5.0)	0.640
Education: Low	82 (80.4)	24 (82.7)	25 (86.2)	32 (80.0)	0.225
Visual accuity: Right eye	0.95 (0.1)	0.95 (0.1)	0.52 (0.3)	0.29 (0.2)	<0.001
Visual accuity: Left eye	0.96 (0.1)	0.94 (0.1)	0.57 (0.2)	0.35 (0.1)	<0.001
Macular edema: Present	-	-	20 (60.6)	13 (39.4)	<0.001

* Data are presented as mean (standard deviation) for age, and visual acuity; frequency (%) for all other variables. Frequency is based on the total number of participants for each item and varies depending on missing data for a specific item. P-values were calculated using ANOVA for continuous variables and chi-square for categorical variables. Self-reported co-morbidities (Health problems other than DM).
** Bold values are the groups that generate the significance.
*** Visual acuity (Snellen)

creatinin levels were 0.80(±0.4) mg/dl, 0.862(±0.2) mg/dl, 1.476(±1.3) mg/dl, 1.464(±0.8) mg/dl (p<0.001); mean FBG levels were 158.60(±68.8) mg/dl, 156.69(±63.5) mg/dl, 207.14(±107.1) mg/dl, 173.45(±65.4) mg/dl (p=0.019) in control group, mild NPDR, moderate-severe NPDR and PDR groups respectively (Table 2).

DM duration was 86.49(±76.1), 163.14(±94.6), 180.52(±85.3) and 221.86(±103.7) months respectively in control group, mild NPDR, moderate-severe NPDR and PDR groups (p<0.001) (Table 2).

There was no difference between the groups in terms of utilisation of diabetes medicines (p=0.225). Table 3 shows VFQ scores according to DR. VFQ composite score (p<0.001), general vision (p=0.001), social functioning (p=0.033), mental health (p<0.001), role difficulties (p=0.001), dependency (p=0.015), color vision (p=0.035) and peripheral vision (p=0.036) were lower at DR patients. However, there was no significant difference seen regarding general health (p=0.664), ocular pain (p=0.061), near activities (p=0.339), distance activities (p=0.137) and driving (p=0.231) . ME, comorbidity, DM duration, FBG, HbA1c, BUN, creatinin and DR were used in logistic regression model. VFQ composite score was divided from 50% to form a dichotomous variable. VFQ score was related with PDR and ME (β= 2.587; p=0.012 and β= 3.581; p=0.036). VFQ composite scores were lower at patients with PDR or ME (Table 4).

The patients which had cataract or undergone cataract surgery were checked. Axial length were measured in all patients and control groups. There was no significant difference between the phacic, cataract and pseudophacic groups regarding the VFQ scores.

4. DISCUSSION

Health related quality of life is a widely used indicator to measure the prognosis of chronical disease. On the other hand, chronic diseases have many important eye

Table 2. *Blood values of study groups (N=200)*

Variables*	Controls	Mild NPDR	Severe NPDR	PDR	p-value
HbA1c (%)	7.612 (1.9)	7.921 (1.6)	8.931 (2.0)	8.148 (1.7)	0.009
BUN**	34.97 (13.2)	32.03 (10.8)	50.64 (42.1)	41.83 (16.1)	0,001
Creatinin**	0.80 (0.4)	0.862 (0.2)	1.476 (1.3)	1.464 (0.8)	<0.001
FBG**	158.60 (68.8)	156.69 (63.5)	207.14 (107.1)	173.45 (65.4)	0.019
DM duration**	86.49 (76.1)	163.14 (94.6)	180.52 (85.3)	221.86 (103.7)	<0.001

* Data are presented as mean (standard deviation) for all variables.
P-values were calculated using ANOVA for continuous variables and chi-square for categorical variables.
** The units are mg/dl for BUN, creatinin and FBG; month for DM duration

Table 3. *VFQ scores according to diabetic retinopathy*

Variables	Controls	Mild NPDR	Severe NPDR	PDR	p-value
VFQ composite	70.33 (18.2)	68.57 (19.3)	60.03 (20.8)	53.07 (23.4)	<0.001
VFQ Subsales					
General Health	34.07 (20.3)	29.46 (20.5)	23.91 (17.6)	26.57 (29.2)	0.664
General Vision	87.80 (18.7)	80.71 (16.8)	64.34 (14.7)	66.21 (32.8)	0.001
Ocular Pain	64.01 (24.3)	62.05 (25.8)	55.98 (26.4)	61.06 (26.9)	0.061
Near Activities	69.41 (27.4)	68.75 (21.4)	58.33 (25.5)	64.02 (34.9)	0.339
Distance Activities	73.26 (27.2)	73.51 (30.3)	63.04 (33.9)	61.49 (30.4)	0.137
Vision Specific:					
Social Functioning	86.26 (21.0)	80.36 (30.7)	69.57 (33.5)	76.01 (31.4)	0.033
Mental Health	72.87 (23.7)	71.88 (28.4)	58.69 (28.3)	21.91 (26.0)	<0.001
Role Difficulties	70.05 (25.9)	62.50 (26.6)	47.28 (33.7)	78.03 (31.3)	0.001
Dependency	83.69 (22.5)	77.98 (29.4)	68.48 (34.7)	67.17 (37.6)	0.015
Driving	73.55 (23.8)	73.09 (23.7)	71.26 (10.9)	70.55 (19.2)	0.231
Color Vision	81.19 (22.5)	86.61 (24.9)	72.83 (30.1)	77.34 (33.8)	0.035
Peripheral Vision	78.02 (27.6)	81.25 (26.9)	63.04 (36.8)	65.63 (34.1)	0.036

Table 4. *Relationship of the variables with VFQ composite score*

	β	SE	95.0 CI	p-value
Comorbidity	1.271	0.39	0.59 : 2.73	.538
DM duration	1.001	.002	0.99 : 1.01	.574
FBG	0.993	.004	0.99 : 1.00	.060
HbA1c	1.104	0.144	0.83 : 1.46	.493
BUN	0.982	0.015	0.95 : 1.01	.215
Creatinin	0.886	0.301	0.49 : 1.60	.689
DR_no				
DR_mild NPDR	2.101	0.549	0.72 : 6.16	.176
DR_severe NPDR	3.945	0.772	0.87 : 17.92	.076
PDR	4.587	0.609	1.39 : 15.13	.012
Macular edema	1.58	0.601	1.01 : 3.26	.046

*CI: Confidence Intervals

symptoms that are not included in health related quality of life scales. NEI-VFQ is a novel scale that can measure eye complications related to chronic diseases.[19] Literature shows decreased scores in NEI-VFQ domains in 10 year follow-up.[21] VFQ questionnaire was found superior to other methods for determining vision related quality of life for patients with DRP.[22] We aimed to screen all components of diabetic disease that can affect visual function.

FBG and HbA1c were used to show diabetic exposure on vision quality in DR.[23-25] In this study we would like to show more indicators that can be a predictor of retinopathy development. NEI-VFQ was used for the comparison of three different groups of DR: mild NPDR, severe NPDR, PDR and the control group. The sociodemographical features of the groups were similar which minimizes the confounding effect of environmental factors ($p<0.05$).

Vision function decline due to living with DM longer can be a good marker of severe DR development. Yau et al. used a pooled analysis data from population-based studies all around the world to find the risk factors of DR. They reported that, DR prevalence end point increased with duration of diabetes and HbA1c levels.[26]

Self reported QOL scales are used in several chronic diseases. NEI-VFQ scale is used both as a composite score and as subscales. Clinicians can diagnose the impaired daily functions of patients by using VFQ scale particularly in chronic diseases. In our study, VFQ composite score decrease were associated with severe DR. VFQ scores was lower in patients with DR. Patients with PDR had the lowest VFQ scores ($p<0.001$) (Table 3). There was a significant decrease in subscales of general vision, social functioning, role difficulties, color vision and peripheral vision in patients with severe NPDR. Sixty one percent of NPDR patients had ME. ME can be associated with the lowest scores in VFQ-25 subscales. In PDR the highest decline seen in mental health and dependency subscales. These findings are in concordance with the results of recent studies that show the significant effect of DR type on VFQ-25 scores.[27] VFQ-25 analysis showed that there was a relationship with visual impairment in patients with DR in most of the subscales. It seems reasonable to suppose that visual impairment affected those subscales. This is a confirmation of the fact that, vision has an impact on daily life activities from the patient's perspective.

One item of VFQ is related to visual field. Some articles reported discrepancy between VFQ scores and clinical manifestations of DR related QOL. In line with our results (Table 3) it can be suggested that the NEI-VFQ-25 score shouldn't be used alone as it is effected from psychological factors. This can be seen in our results on Table 3. Also, multiple eye diseases can show synergistic or may be additive effect which can be related to patient's reports. Their report on first eye disease may be different than reports on next pathologies.[28] Hirneiss et al. used combination of cup/disc ratio and VFQ, refraction tests and VFQ, intraocular pressure or the ocular pain subscale of the NEI-VFQ-25 or with clinical biomarkers and VFQ to exclude prevalent eye diseases.[29]

The contradiction about the affectibility of VFQ from the other parameters were also tried to be solved by using the logistic model. Cataract or the other comorbidities can be presented with vision functionality loss. In this study we didn't include patients with glaucoma, uveitis or vitreoretinal manipulations like panretinal or grid laser, intravitreal enjections or vitreoretinal surgery. We checked the patients who had cataract or undergone cataract surgery. There was no significant difference between the phakic, cataract and

pseudophakic groups. Also DM duration and its effect on visual funcionality were key points . The model consisted of the duration, and the diabetic biomarkers together with the DR types. It was clearly seen that ME and PDR were the only significant parameters that affect VFQ scores following the advanced analyses ($p<0.05$). PDR was the only category that shows independent association with lower vision related QOL (Table 4). In a cross sectional study, Granström T.[30] et al found that diabetic patients with visual impairment had a very low score for the VFQ-25 subscale of general health. In another cross sectional study, VFQ score decline at bilateral PDR was higher than unilateral moderate NPDR and bilateral moderate NPDR.[27] Our study was conducted in a referee hospital that can give an important point of view to ophthalmologists. Overall, the patient demographics, clinical characteristics, and visual functioning in our clinical study were comparable with large studies. On the other hand all DM patients didn't recruit to the study due to financial problems. Altough the results represent a substantial portion of the DR and DM patients, attention must be paid when reading the interpretations. DR prevalence in Turkish population is still unknown. New studies are needed to determine retinopathy prevalence in diabetics.

In conclusion, the association with vision-specific QOL increases with the severity of DR. Individuals with PDR had poorer scores to less severe DR. Chronic diseases are usually thought to be limited to systemic involvement but visual involvement especially DR formation should also be monitored at routine follow-up. VFQ-25 is an effective instrument to measure the QOL of at DM patients at ophthalmology practices.

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