Diabetes Ther (2023) 14:205–217
https://doi.org/10.1007/s13300-022-01348-3

ORIGINAL RESEARCH

Single-Field Fundus Photography for Screening of Diabetic Retinopathy: The Prevalence and Associated Factors in a Population-Based Study

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Received: October 22, 2022 / Accepted: November 23, 2022 / Published online: December 8, 2022

ABSTRACT

Introduction: We aimed to determine the prevalence and risk factors for diabetic retinopathy (DR) in a multi-primary healthcare facilities-based DR screening project by analyzing single-field fundus photographs among patients with diabetes in Rafsanjan City, Iran, based on the Rafsanjan Cohort Study, as a part of the prospective epidemiological research studies in IrAN (PERSIAN).

Methods: Of all participants in the Rafsanjan Cohort Study (performed in four primary healthcare facilities across Rafsanjan City from August 2015 to December 2017), patients with diabetes were recruited in this study. All participants underwent a standardized interview and clinical and paraclinical examinations for demographic characteristics, and medical conditions according to the PERSIAN's protocols. In addition, digital fovea-centered and single-field fundus photography was performed for DR identification and grading. For assessment of agreement, a subgroup of participants underwent fundus examination, randomly. DR was graded as nonproliferative (NPDR) or proliferative (PDR).

Results: Of 8414 screened participants, 1889 had diabetes. The total prevalence of DR was 6.93% [131 individuals including 110 (5.82%) with NPDR, and 21 (1.11%) with PDR] based on single-field fundus photographs, with almost perfect agreement with fundus examinations ($\kappa = 0.82$). On adjusted multivariate analysis, duration of diabetes (OR 1.16, 95% CI 1.13–1.19), positive family history for diabetes (OR 1.73, 95% CI 1.09–2.75), fasting plasma glucose (FPG) $\geq$ 126 mg/dL (OR 1.98, 95% CI 1.16–3.39), and serum creatinine level (OR 1.79, 95% CI 1.08–2.98) were associated with DR. Factors including age, education level, physical activity, body mass index, hypertension, and cardiovascular and renal diseases did not have association with DR on adjusted multivariate analysis.

Conclusions: Single-field fundus photography can be used for screening of DR in primary healthcare facilities. In individuals with diabetes, duration of diabetes, positive family history for diabetes, FPG $\geq$ 126 mg/dL, and serum creatinine level may be associated with DR.

Keywords: Diabetes; Diabetic retinopathy; Prevalence; Risk factor; Prospective

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Key Summary Points
The prevalence of diabetes in Rafsanjan City, Iran, is estimated 19.1%, and this is the first study to report the prevalence of diabetic retinopathy (DR) in this city.
This population-based study assessed the prevalence of diabetic retinopathy (based on fundus photography, as an available and effective screening tool) and its associated factors.
Single-field fundus photography is sufficient for screening of diabetic retinopathy in comparison with fundus examinations.
Duration of diabetes, family history positive for diabetes, FPG $\geq$ 126 mg/dL, and serum creatinine level may be associated with diabetic retinopathy.

INTRODUCTION

Visual impairment due to uncontrolled diabetes has shown an increasing trend worldwide, affecting quality of life. Diabetic retinopathy (DR) occurs in approximately three-fourths of patients with diabetes two decades after diagnosis of the disease [1]. The prevalence of DR in patients with diabetes varies among different populations [2–7]. In Iran, the prevalence of DR in population-based studies is estimated at 29.6% [8].

To decrease the burden of DR, current guidelines recommend that, for type 1 diabetes, a dilated fundus examination be performed 3–-5 years after the diagnosis and then annually. In type 2 diabetes, the first dilated fundus examination should be done upon the diagnosis and annually thereafter [9]. These regular screenings are suggested for DR detection at early stages to prevent severe retinal complications [10]. Despite these serial examinations, DR remains a leading cause of irreversible visual impairment [11]. In addition, this approach is labor intensive and costly. Therefore, performing alternative screening techniques including fundus photography seems logical [12, 13]. Multiple- and even single-field images are reliable and cost-effective screening tools for DR [14–16].

Factors that play a role in the development of DR include duration of diabetes, glycemic control, and urinary albumin [4, 17, 18]. Here, we conducted a study in Rafsanjan City, Kerman Province, Iran, using data from the Rafsanjan Cohort Study (RCS) to evaluate the prevalence of DR (based on single-field fundus photographs) and its associated factors. The characteristics of Rafsanjan City and its population are described elsewhere [19]. The prevalence of diabetes among this population is relatively higher (19.1%) than the mean of Iranian population [20].

METHODS

Study Design and Patient Selection

This cross-sectional study was conducted on the participants of RCS, as a part of the prospective epidemiological research studies in IrAN (PERSIAN). Rafsanjan is a city in the southeast of Iran. RCS is also part of the PERSIAN Eye Cohort Study (including five other cities in Iran) for determining the prevalence of and factors associated with major ocular diseases including DR. The details of the PERSIAN and the RCS profiles are described elsewhere [10, 11, 19, 21]. A total of 9990 individuals (5335 female and 4655 male) aged between 35 and 70 years from four urban and suburban areas of Rafsanjan City during August 2015 to December 2017 participated in this study according to the PERSIAN's protocols [21]. The ethics committee of Rafsanjan University of Medical Sciences approved this study (ethics code IR.RUMS.REC.1400.122). In addition, this study was performed in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants.

Data Collection

All participants underwent a self-reporting standardized interview to complete validated questionnaires containing questions on demographics, dietary intake, and medical and habitual history. Questionnaires were validated in the PERSIAN [21].

Diabetes was diagnosed at fasting plasma glucose (FPG) of ≥ 126 mg/dL, or if a patient was receiving blood glucose-lowering treatment [22, 23]. The duration of diabetes was recorded in years. The duration of diabetes in newly diagnosed patients was considered as zero years. History of diabetes was defined as the proportion of individuals with diabetes who were aware of their diabetes at the time of participating in the study [22].

Blood pressure and anthropometric indices were also assessed. Blood pressure was measured in a supine position in the right arm, using a standard mercury sphygmomanometer, using the first and fifth Korotkoff sounds to the nearest 2 mmHg. Participants rested for 10 min before testing [24]. Hypertension was defined as present if systolic blood pressure (SBP) was ≥ 140 mmHg, diastolic blood pressure (DBP) was ≥ 90 mmHg, or the participant reported current treatment for hypertension [25]. Mean arterial pressure (MAP) was calculated as DBP + 1/3 (SBP-DBP) [26]. Height and weight were measured in light clothing by a trained observer. Body mass index (BMI) was calculated as weight (kg)/height (m^2) [27]. FPG, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, blood urea nitrogen (BUN), creatinine, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) were measured using a Biotecnica analyzer (BT 1500, Italy) at the central laboratory in cohort center of Rafsanjan City. Glomerular filtration rate (GFR) was calculated as (140 − age) × (weight) × (0.85 if female)/(72 × serum creatinine) [28].

One trained optometrist took ocular history including any previous ocular surgery or retinal laser therapy from all participants. She measured uncorrected distance visual acuity (UDVA), cyclorefraction, and corrected distance visual acuity (CDVA). Then after pupillary dilation, fundus photography was done, for all participants. These photographs were taken using Topcon TRCNW6S (Topcon America Corp., Paramus, NJ, USA) fundus camera with a single-field 45° digital color retinal image (effective size of 64 megapixels) centered on the fovea. If the quality of the image was insufficient, it was retaken. If the retaken image had still a poor quality, the photograph was considered ungradable and the patient was referred for clinical examinations. Images were stored as uncompressed tagged image format files (TIFF) and were displayed on a standard 17-inch monitor. One ophthalmologist (A.Z.) graded the fundus photographs for DR. Randomly, 331 (17.52%) patients with diabetes underwent dilated fundus examination by +90 diopter lens by one ophthalmologist (M.S.) for assessment of agreement for DR identification and grading between examination and photography.

The patients with diabetes were divided into three different grades for DR: (1) no DR, (2) nonproliferative DR (NPDR; i.e., presence of dot-blot hemorrhages, cotton-wool spots, venous beading, or intraretinal microvascular anomalies in the absence of neovascularization), and (3) proliferative DR (PDR; i.e., neovascularization of the disk, elsewhere of the retina or iris, or vitreous hemorrhage) [29]. Patients with evidence of regressed or treated PDR including previous pan-retinal photocoagulation or vitrectomy due to complicated PDR were categorized as having PDR, too. This grading was based on the worst eye and was applied for evaluations of fundus photographs and clinical examinations.

Patients with presence of macular edema were referred for macular optical coherence tomography (OCT) for confirmation. The definitions for diabetic macular edema (DME), including clinically significant macular edema (CSME) on fundus photographs, are described elsewhere by the Multi-Ethnic Study of Atherosclerosis (MESA) and the National Health and Nutrition Examination Survey (NHANES) [30, 31].

Statistical Analysis

Chi-square test was used to analyze categorical variables across DR categories. *t*-Test was used to compare continuous variables among the groups. In addition, we used univariate and multivariate analysis to determine the odds ratios (ORs) and the corresponding 95% confidence intervals (CI) for the relation of DR with selected risk factors. Potential risk factors variables were introduced sequentially into the models. The adjusted model included age (continuous variable), education years (continuous variable), BMI (continuous variable), hypertension (yes/no), cardiovascular diseases (yes/no), renal disease (yes/no), diabetes duration (continuous variable), family history of diabetes (yes/no), physical activity level (continuous variable), FPG $\geq$ 126 (yes/no), and creatinine (continuous variable). Kappa values were calculated and interpreted according to the Landis and Koch classification (0–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, almost perfect) [32]. All analyses were performed using SPSS software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY). All p values are two-sided, and p values < 0.05 and 95% confidence intervals were considered as statistically significant.

RESULTS

Demographic, Selected Medical, and Laboratory Characteristics of Participants

From the 9990 participants, 8414 individuals had complete charts and enrolled for diabetes screening. Among this population, 22.45% (1889) had diabetes. Of the participants with diabetes, 82.48% (1558) had history of diabetes and 17.52% (331) were newly diagnosed with diabetes at the time of participating in the study.

Mean age was 55.36 ± 8.22 years. Females accounted for 60.40% of the sample. The mean number of education years was 6.93 ± 5.08. For all patients (1889), mydriatic single-field fundus photographs were taken. Grading of DR was done according to the fundus photographs, as described in detail in the methods section. In addition, 331 (17.52%) individuals were selected randomly for dilated complete fundus examination to evaluate the agreement between the photography and the examination. Just 11 patients had disagreement between photography (no DR) and examination (minimal or mild NPDR). We showed almost perfect agreement in detecting DR and its severity between these two methods ($\kappa = 0.82$). Ophthalmic examinations of seven patients with ungradable photographs revealed media opacities (including corneal scar, significant cataract, or dense vitreous hemorrhage). Of the patients, 6.93% (131) had retinopathy. The prevalence of NPDR and PDR (regardless of retinal laser treatment) was 5.82% (110) and 1.11% (21), respectively. Evidence of macular edema was present in 2.17% (41) of them. The characteristics of the participants (in total and according to retinopathy status) are presented in Table 1. Subjects with DR (compared with those without DR) had the following characteristics: older age, lower mean of education level and BMI, higher duration of diabetes, positive family history for diabetes, histories of diabetes treatment, hypertension, cardiovascular and renal diseases, lower mean of physical activity, higher mean of FPG, BUN, creatinine, and ALP, and lower mean of LDL, SGPT, and GFR (all $p < 0.05$).

From the respondents, 81.40% were under treatment (with oral agents and/or insulin) for diabetes currently. Overall, diabetes duration was 5.08 ± 6.07 years. Patients with PDR had longer duration of diabetes compared with the individuals with NPDR (17.24 ± 5.54 versus 12.47 ± 7.99 years, respectively, $p = 0.01$), but mean of FPG was not different between PDR and NPDR participants (200.48 ± 63.94 versus 204.30 ± 77.38 mg/dL, respectively, $p = 0.83$).

Multivariate Analysis for Diabetic Retinopathy by the Selected Risk Factors

For multivariate analysis, age, education level, BMI, hypertension, cardiovascular and renal diseases, duration of diabetes, diabetic

Table 1 Demographic, selected medical and laboratory characteristics of diabetic participants according to retinopathy status

Characteristics	Total (N = 1889)	Retinopathy (N = 331)	No retinopathy (N = 1558)	p value
Age (years)	55.36 ± 8.22	58.53 ± 6.33	55.12 ± 8.29	< 0.001
Female, N (%)	1141 (60.40)	80 (61.07)	1061 (60.35)	0.872
Education level (years)	6.93 ± 5.08	5.66 ± 4.97	7.03 ± 5.07	0.003
BMI (kg/m^2)	29.20 ± 4.77	28.35 ± 4.50	29.27 ± 4.79	0.035
MAP (mmHg)	86.18 ± 11.36	87.18 ± 11.43	86.10 ± 11.36	0.295
Hypertension, N (%)	898 (47.59)	74 (56.49)	824 (46.92)	0.034
Cardiovascular diseases, N (%)	366 (19.40)	39 (29.77)	327 (18.62)	0.002
Renal diseases, N (%)	17 (0.93)	4 (3.05)	13 (0.074)	0.007
Diabetes duration (years)	5.08 ± 6.07	13.24 ± 7.82	4.48 ± 5.46	< 0.001
Diabetic treatment, N (%)	1536 (81.40)	130 (99.24)	1406 (80.07)	< 0.001
Positive family history for diabetes, N (%)	1208 (64.02)	100 (76.34)	1108 (63.10)	0.002
Current habitual history				
Cigarette, N (%)	395 (20.98)	22 (16.79)	373 (21.29)	0.223
Opium, N (%)	394 (20.92)	27 (20.61)	367 (20.95)	0.927
Alcohol, N (%)	124 (6.59)	5 (3.82)	119 (6.79)	0.185
Dietary macronutrient components				
Carbohydrate (g/day)	71.70 ± 4.29	71.62 ± 4.16	71.71 ± 4.30	0.835
Lipid (g/day)	12.48 ± 3.17	12.60 ± 3.22	12.47 ± 3.17	0.644
Sum of carbohydrate and lipid (g/day)	84.18 ± 2.07	84.22 ± 2.16	84.17 ± 2.07	0.784
Physical activity level	37.65 ± 5.37	36.54 ± 4.22	37.73 ± 5.44	0.014
FPG (mg/dL)	159.93 ± 58.95	203.69 ± 75.17	156.66 ± 56.24	< 0.001
Lipid profile				
Triglyceride (mg/dL)	198.31 ± 141.17	209.82 ± 191.39	197.45 ± 136.73	0.333
LDL (mg/dL)	103.50 ± 33.94	97.39 ± 39.55	103.96 ± 33.45	0.033
HDL (mg/dL)	57.10 ± 10.84	56.35 ± 10.56	57.15 ± 10.86	0.418
Cholesterol (mg/dL)	198.09 ± 43.86	192.45 ± 52.66	198.51 ± 43.12	0.127
Renal function tests				
BUN (mg/dL)	14.43 ± 4.53	15.95 ± 5.73	14.32 ± 4.41	< 0.001
Creatinine (mg/dL)	1.05 ± 0.026	1.13 ± 0.40	1.04 ± 0.24	< 0.001
GFR (mL/min)	68.39 ± 12.48	63.66 ± 14.03	68.74 ± 12.29	< 0.001

Table 1 continued

Characteristics	Total (N = 1889)	Retinopathy (N = 331)	No retinopathy (N = 1558)	p value
Liver function tests				
SGOT (U/L)	20.04 ± 12.02	18.12 ± 7.87	20.19 ± 12.26	0.058
SGPT (U/L)	23.74 ± 17.31	20.82 ± 10.98	23.96 ± 17.68	0.045
ALP (U/L)	240.36 ± 68.81	252.48 ± 71.34	239.43 ± 68.55	0.036
GGT (U/L)	32.98 ± 28.59	30.60 ± 17.60	33.16 ± 29.24	0.323

Data are mean ± SD or number (percentage)

N number, *BMI* body mass index, *MAP* mean arterial pressure, *FPG* fasting plasma glucose, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *BUN* blood urea nitrogen, *GFR* glomerular filtration rate, *SGOT* serum glutamic-oxaloacetic transaminase, *SGPT* serum glutamic pyruvic transaminase, *ALP* alkaline phosphatase, *GGT* gamma-glutamyl transferase

treatment, positive family history for diabetes, physical activity, FPG ≥ 126, and serum creatinine level were entered into a logistic regression model. Age, hypertension, cardiovascular and renal diseases, duration of diabetes, positive family history for diabetes, FPG ≥ 126, and serum creatinine level were shown to be independently associated with diabetic retinopathy. On the adjusted analysis, duration of diabetes, positive family history for diabetes, FPG ≥ 126 mg/dL, and serum creatinine level were associated with diabetic retinopathy. Each additional year of diabetes duration was associated with 16% higher odds of having DR (OR 1.16; 95% CI 1.13–1.19). Adjusted odds of having DR were 1.73 times higher among participants with positive family history for diabetes compared with patients with no history (OR 1.73; 95% CI 1.09–2.75). Adjusted odds of having DR were 1.98 times higher among those who had FPG ≥ 126 mg/dL compared with patients with FPG < 126 mg/dL (OR 1.98; 95% CI 1.16–3.39). Each additional mg/dl of serum creatinine level was associated with 79% higher odds of having DR (OR 1.79; 95% CI 1.08–2.98). The effects of other factors such as age, hypertension, and cardiovascular and renal diseases dissipated in the adjusted model (Table 2).

DISCUSSION

The study showed that the prevalence of diabetic retinopathy was 6.93% among diabetic patients in Rafsanjan City. In a systematic review by Maroufizadeh et al. [7], the prevalence of diabetic retinopathy in Iran (including general population, diabetic and eye clinics) was reported as 41.9% (95% CI 35.6–48.2). In another systematic review, the pooled prevalence of DR in population-based studies in Iran was 29.6% (95% CI 22.6–36.5) [8]. They showed that the rate was 31.8% (95% CI 24.5–39.2) in diabetic clinics and 57.8% (95% CI 50.2–65.3) in eye clinics. In the adjacent countries of Iran, prevalence of DR was 36.2% in Armenia [6] and 46.0% in Russia [33]. In other Asian countries, the prevalence of DR varied between 10.5% and 44.7% [3, 5, 34–38]. In Western countries, that is, Australia, the UK, and the USA, the prevalence of DR is reported as 15.3%, 19%, and 28.5% respectively [2, 4, 39]. The prevalence of DR in this study was lower than the mentioned rates. The lower rate of DR in this study can be explained by relatively short duration of diabetes among participants (5.08 ± 6.07 years), compared with previous studies. In addition, 17.52% had new onset diagnosis of diabetes. Other causes of these differences in DR prevalence are difference in methodology (including the screening tool; the prevalence may be

Table 2 Odds ratios (95% confidence interval) for diabetic retinopathy by the selected risk factors

Risk factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (years)	1.06 (1.03–1.08)	1.02 (0.98–1.05)
Education level (years)	0.95 (0.91–0.98)	0.96 (0.92–1.00)
BMI (kg/m^2)	0.96 (0.92–1.00)	0.98 (0.94–1.03)
Hypertension	1.47 (1.03–2.10)	0.97 (0.64–1.49)
Cardiovascular diseases	1.85 (1.25–2.75)	1.27 (0.80–2.01)
Renal diseases	4.22 (1.36–13.14)	3.48 (0.95–12.73)
Diabetes duration (years)	1.17 (1.14–1.20)	1.16 (1.13–1.19)
Positive family history for diabetes	1.89 (1.25–2.86)	1.73 (1.09–2.75)
Physical activity	0.95 (0.91–0.99)	0.96 (0.92–1.01)
FPG $\geq$ 126 mg/dL	2.03 (1.26–3.28)	1.98 (1.16–3.39)
Creatinine (mg/dL)	2.29 (1.36–3.87)	1.79 (1.08–2.98)

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *FPG* fasting plasma glucose

underestimated by single-field photography in comparison with complete fundus examination or seven-field photography) [16, 40, 41], setting and risk of selection bias (the prevalence is the lowest in general population, primary healthcare facilities, diabetic or eye clinics, and hospitals) [7, 8], diagnostic method (diagnosis of diabetes based on patient self-report, without laboratory testing, may overestimate the prevalence of DR due to the exclusion of undiagnosed diabetes from the sample) [8], sample size, ethnicity (ethnic variations may be due to related social and economic differences and access to diabetes care) [42], nutrition, demographic, and lifestyle [4].

A large number of patients with diabetes do not receive appropriate ophthalmic examinations for early detection and management of DR [43, 44]. A variety of alternative techniques can be performed to identify and classify DR, including mydriatic or nonmydriatic photography [40]. Seven-field stereoscopic color photography is the gold standard for the detection and classification of DR, as suggested by the Early Treatment Diabetic Retinopathy Study (ETDRS) group [45]. However, this technique requires high-tech photography devices, film processing, skilled photographers, and expert photograph readers [14]. A systematic review by Williams et al. [14] demonstrated that single-field fundus photographs in individuals with diabetes can be considered as a reliable screening tool for detection of DR in primary healthcare services. In addition, Lin et al. [46] showed excellent agreement ($\kappa = 0.97$) between the single-field nonmydriatic fundus photography and seven-standard field photographs for the degree of DR. Ku et al. [47] showed moderate agreement ($\kappa = 0.67$) between the single-field mydriatic fundus photography and dilated fundus examination for any grades of DR among 360 patients. Here, we used single-field mydriatic fundus photography as the screening tool for DR identification, and also grading with acceptable agreement with dilated fundus examination ($\kappa = 0.82$). Our calculated kappa value was higher than that reported by Ku et al. [47]. This difference may be due to different imaging devices and techniques, photograph resolution, and also factors that can affect the quality of images, including media opacities [14].

With age, chances of getting DR and its severity increase in patients with diabetes [39, 48, 49]. Some authors suggest that age might be a surrogate marker of duration of DR

in patients [17]. In this study, although age was associated with DR on unadjusted analysis, but this association was not significant on adjusted multivariate analysis.

Diabetic education programs will help patients to improve their awareness about different aspects of diabetic retinopathy [50, 51]. Previous studies showed patients with lower educational level had a higher risk for DR, similarly to our findings [52, 53].

The duration of diabetes in the present study was strongly associated with DR, similar to previous literature [3, 4, 6]. Studies have revealed that the duration of diabetes might reflect glycemic control over time [4].

In a study by Maghbooli et al. [54], the investigators showed that family history of diabetes was associated with DR. They suggest that DR may have genetic and epigenetic basis. Similarly, in this study we revealed that positive family history for diabetes in first-degree relatives was associated with higher risk of DR. The familial clustering of diabetic complications (including DR) could result from a combination of genetic factors and environmental exposures (including lifestyle characteristics) [55].

Most studies showed positive association between high BMI with DR [56–58], while other studies revealed contradictory results [6, 17, 59–61]. Our study found no statistically significant association between BMI with DR on multivariate analysis.

Previous studies have shown that hypertension and high SBP are risk factors for DR [38, 39, 62, 63]. In this study, unadjusted multivariate analysis revealed hypertension to be a risk factor for DR, but this correlation was not confirmed on adjusted multivariate analysis.

Several studies have shown a significant association between having chronic noncommunicable diseases (renal and heart diseases) and DR [2, 64]. However, in our study, this association was not proven on multivariate analysis. It is possible that our analysis failed to reveal the association between chronic noncommunicable diseases and DR because we used self-reported data on these conditions instead of data obtained from medical records.

Results of previous studies were not consistent for the association of smoking or alcohol consumption with DR [4, 6, 62, 63, 65–68]. In this study, no significant associations were found between cigarette, alcohol, or opium consumption and DR.

Previous studies have shown association of high total caloric intake with higher risk of DR [69]. Another study reported that risk of DR was higher in patients with higher consumption of rice [70]. However these associations were not found in the present study.

The reported associations of physical activity with retinopathy have not been consistent [6, 71, 72]. In this study, we found physical activity was not statistically significant associated with DR on multivariate analysis.

Previous studies showed that the incidence of diabetic retinopathy was significantly associated with elevated baseline FPG levels [4, 73]. Similarly, we found participants with current FPG $\geq$ 126 mg/dL had higher risk for DR development. Previous studies showed that higher BUN and creatinine were associated with DR [3, 74]. In agreement these studies, we showed that higher BUN, creatinine, and GFR were associated with DR on univariate analysis. In addition, higher creatinine level was associated with higher risk of DR on multivariate analysis. However, on univariate analysis, serum LDL, SGPT, and ALP were associated with DR, but these associations have not been consistent in previous studies [4, 36, 75–78].

The large sample size with extensive information on potential confounders is one of the main strengths of our study. The adjustment for recognized risk factors of diabetic retinopathy such as demographic, lifestyle, and medical history was another major strength of our investigation. Nonetheless, our study had some limitations. First, the prevalence statistics reported in our study were based on the patients with diabetes who were registered in primary healthcare facilities in Rafsanjan City. It is possible that those who refused or were unable to participate were systematically different from those who were included in the study, particularly in terms of their diabetes status and vision problems. Second, in this study we used single-field and macula-centered fundus photographs for grading of diabetic retinopathy, which may underestimate the severity of retinopathy due

to lack of peripheral retina evaluation. For assessing the importance of this limitation, we compared the results of DR grading according to fundus examinations and photographs, which showed good agreement between these two screening methods, similar to the previous studies. Third, some of the risk factor variables that were used in the study, including chronic noncommunicable diseases, years of having diabetes, habitual history, and physical activity, were based on self-report of the patients due to absence of quality measurements, which may cause recall bias. Fourth, we did not divide participants with diabetes into types 1 and 2 of the disease for further analysis to assess for differences between them.

CONCLUSION

Single-field fundus photography is a sufficient screening tool for identification of DR in primary healthcare facilities. Duration of diabetes, positive family history for diabetes, FPG $\geq$ 126 mg/dL, and serum creatinine level may be associated with DR.

ACKNOWLEDGEMENTS

We thank the people who participated in the study, the study-site personnel, and members of the Rafsanjan cohort center in Rafsanjan, Iran.

Funding. The Iranian Ministry of Health and Medical Education has contributed to the funding used in the PERSIAN Cohort through Grant no 700/534. This study has also been supported by the Vice Chancellery for Research & Technology of Rafsanjan University of Medical Sciences. The context of this article are the views of the authors and the funder had no role in design of the study and collection, analysis, and interpretation of data, decision to publish and writing the manuscript.

Authors' Contributions. Authors are Mohammadreza Soleimani (MS), Fateme Alipour (FA), Yousef Taghavi (YT), Marjan Fatemipour (MF), Hamid Hakimi (HH), Zahra Jamali (ZJ), Parvin Khalili (PK), Fatemeh Ayoobi (FAy), Maryam Sheikh (MSh), Roya Tavakoli (RT) and Amin Zand (AZ). MS, AZ and HH designed the study and supervised the project. AZ reviewed the photographs. MS performed ophthalmic examinations. RT performed optometric examinations. MSh took photographs. ZJ, FAy and MSh collected the data. AZ and ZJ prepared tables. PK performed the statistical analysis. AZ, FA, YT, MF, HH and ZJ wrote and revised the main manuscript text. All the authors read and approved the final manuscript.

Disclosures. Mohammadreza Soleimani, Fateme Alipour, Yousef Taghavi, Marjan Fatemipour, Hamid Hakimi, Zahra Jamali, Parvin Khalili, Fatemeh Ayoobi, Maryam Sheikh, Roya Tavakoli and Amin Zand have nothing to disclose. None of the authors has any financial interest in the subject matter of this paper.

Prior Publication. This manuscript has not been previously presented or published.

Compliance of Ethics Guidelines. The ethics committee of Rafsanjan University of Medical Sciences approved this study (Ethical codes: ID: IR.RUMS.REC.1400.122). Written informed consent was obtained from the participants. The data of participants kept confidential and was only accessible to the study investigators. All methods were carried out in accordance with relevant guidelines and regulations.

Data Availability. The datasets used during the current study are available on the PERSIAN Adult Cohort Study Center, Rafsanjan University of Medical Sciences, Iran. The data is not available publicly due confidentiality. However, upon a reasonable request, the data can be obtained from the corresponding author.

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