Influencing factors of vision-threatening disease among patients with diabetes in the central region of Saudi Arabia: A case–control study

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ABSTRACT

Aims: Diabetic retinopathy is called as vision threatening disease. It affects retina very severely. DR is a common public health problem in Worldwide. Our main objective was to identify significant risk factors for diabetic retinopathy among diabetes mellitus patients. Materials and Methods: The present retrospective Case-Control study was conducted with 404 DM patients' records were collected from King Abdulaziz Medical City, Riyadh, Saudi Arabia. Statistical analysis used: Data were presented as descriptive statistics, multivariate logistic regression, association between variables was using odds ratio and 95% confidence interval. Results: Among 404 diabetes patients, 192 (47.5%) were Cases and 212 (52.5%) Controls. In multivariate regression analysis showed that male gender also had a higher likelihood in the development of DR, OR: 1.68 [95% CI: (1.04 – 2.71); p<0.05]. Patients with poor glycaemic control, OR: 4.86 [95% CI: (2.21-10.66); p<0.001]. Similarly, HbA1C, Low LDL was prominent risk factor in the progression of DR except age, hypocholesterolaemia, nephropathy wasn’t significant. Conclusions: From our study findings, male gender, tobacco habit, poor glycaemic control, and Low HDL were appeared independently associated with the development of vision-threatening disease. By regular check-up, reducing risk factors or retain their stages in the same stage or to prolong the DR incidents among DM patients.

Keywords: Case–Control Study, diabetes mellitus, diabetic retinopathy, risk factors

Introduction

Diabetes mellitus (DM) is a common and prevalent disease at a global level.[1] DM causes diabetic retinopathy (DR). DR causes slow damage to the retina, the light-sensitive lining at the back of the eye. Diabetes impacts the body’s capability to use and keep glucose. The disease is diagnosed when too much glucose is detected in the blood, which can result in damage to various parts of the body, including the eyes.[2] It damages small blood vessels in the retina that leak blood. This causes the retinal tissue to inflate, resulting in cloudy or distorted vision.[3] Both eyes can be affected, and the likelihood of DR is higher with longer duration of diabetes. The most common complication of untreated DR is blindness.[4] According to the National Eye Institute, DR has four stages. The initial stage is nonproliferative DR, where balloon-like swelling occurs in a few...
areas in the retina’s small blood vessels, as shown in Figure 1. The second stage is moderate nonproliferative DR, where blocking occurs in some blood vessels that support the retina. The third stage is severe nonproliferative DR, where more blood vessels become blocked resulting in an interruption of the blood supply to the retina. The fourth stage is proliferative diabetic retinopathy (PDR). PDR means, that the minor blood vessels develop in the back side of the eye ball with fluid. The new blood vessels may leak blood, which may affect vision.

Almost everyone with type I diabetes has nonproliferative retinopathy. Most people with type II diabetes will also get it. However, the retinopathy that destroys the eye is far less common.[5] Several studies have investigated the factors influencing the development of DR among DM patients.[5‑8] Most studies revealed that the following conditions influence the development of DR among DM patients: prolonged duration of DM, worst blood sugar levels, irregular blood pressure and cholesterol levels, pregnancy, and smoking.[5‑8] Some studies in the Gulf investigated the prevalence of DR and the factors predictive of DR risk. The disease was found in 40% of Kuwaiti type II diabetic patients, while 21% reported having sight-threatening retinopathy.[9] A Saudi National Diabetes Registry-based study reported an overall prevalence of DR of 20%, with 9% having nonproliferative DR, 11% having proliferative DR, and 6% having macular edema.[10] The study also reported that the duration of DM and age were the most predictive factors for DR (odds ratio [OR] 8.9 [95% confidence interval [CI]: 8.3–9.5] and OR 5.8 [95% CI: 5.1–6.6], respectively).[10] Higher risk of DR is significantly associated with consistently elevated blood glucose, neuropathy, insulin use, hypertension, and male gender, while the risk is significantly decreased among smokers, obese patients, and those with hyperlipidemia.[5,10] A study in the southern region of Saudi Arabia reported that the prevalence of DM and DR was 22% and 6%, respectively. The study also showed that advanced age (>60 years), insulin therapy, longer duration of diabetes (>10 years), uncontrolled DM, and nephropathy were significantly associated with elevated DR risk. The main objective of our study is to find significant influencing factors for the development of DR among DM patients.

Subjects and Methods

Study Design, Population, and Area

We conducted a case–control study with 404 DM patients with and without DR. Patients’ records were collected during the period of January 2013 - December 2015 was collected from database of King Abdulaziz Medical City, Riyadh.

Sample Size Calculation

For the case and control groups, sample size was determined using OpenEpi. Previous literature revealed that poor glycemic control was 46%[5], OR = 2.23[11] with 95% confidence interval, and with 80% of statistical power, ratio was 1:1 and added 10% for losses, the calculated minimum sample size was 102 in cases and 102 in controls. But, in the present study, we have selected and included 192 patients with DM and DR as cases and 212 patients with DM and without DR as controls.

Collection and Method of Selection of Patients’ Data

Data were collected from patients’ medical database by using simple random sampling method with a predesigned and pre-tested questionnaire. Our questionnaire contained two parts: part 1 consisted of socio-demographic variables and part 2 had various clinical factors related to DM and DR. Data on several demographic variables, such as age, gender, tobacco use, metabolic control like body mass index (BMI), and clinical factors (comorbidities) like glycemic control, hypertension, dyslipidemia, and diabetic nephropathy were collected. In this study, we included patients aged ≥18 years with and without DR and who were the residents of Saudi Arabia; we excluded those who had chronic diseases, communicable diseases, or severe renal diseases.

In the statistical analysis, we analyzed demographic and lifestyle factors and relevant medical conditions associated with DR. In descriptive statistics, the continuous variables were presented as mean and standard deviation and the dichotomous variables were presented as numbers and percentages. To find the risk factors associated with DR, bivariate logistic regression model was used with ORs with 95% CI and P values were obtained to find significance. Once again the demographic and clinical variables’ significances were examined by multivariate logistic regression (MLR) analysis and adjusted ORs with 95% CIs were found. All data were collected, managed, and compiled by MS Office 365 (Microsoft Ltd., USA). Data were analyzed by SPSS 21.0 version (IBM SPSS Ltd., Chicago, IL, USA). P values <0.05 were considered statistically significant.

Ethical Approval and Clearance

This study was conducted after obtaining prior approval and permission (SP16/170/R) from both the research committee of College of Pharmacy and from King Abdullah International Medical Research Centre (KAIMRC) institutional research committee and ethical committee of King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia. Data were collected from patients’ medical database of KAIXMRC and were kept confidential.

Results

We included data of a total of 404 patients and incorporated them in our present study. Among the 404 patients, 192 were cases and 212 were controls. Overall mean age of the patients was 63.7 ± 11.1 (range: 26–94) years, and 202 (50%) were males. Mean age of cases was 63.1 ± 9.2 (range: 40.0–88.0) years and of controls was 64.2 ± 12.5 (range: 26.0–94.0) years. Proportion of females was more in controls (110; 51.9%) than cases (92; 47.9%). Also, 58.0% of cases and 55.7% of controls belonged to the age
group of >60 years. Overall average BMI in both groups was 31.9 ± 8.1 (range: 15.2–127.9) kg/m². Only 4.2% of patients were smokers; 312 (77.2%) had poor glycemic control and 80.0% were hypertensive. Overall mean level of HbA1C was 9.1±2.3%; 48 (11.9%) of patients had HbA1C level ≤6.5% and 356 (88.1%) were >6.5%.

The variables like gender and tobacco use were the risk factors of DR; age and BMI were not associated with the development of DR in bivariate logistic regression analysis, as shown in Table 1. Glycemic control classification (yes, no) and groups showed a significant with P < 0.001, as shown in Figure 2.

Similarly, hypertension and low high-denisty lipoprotein (HDL) showed a significant association with DM with groups DR. In patients, male gender didn’t show significance in the development of DR (OR = 0.85 [95% CI: 0.58–1.26; P = 0.426] with P value >0.05 in univariate analysis, but male gender was a significant factor in the development or progression of DR with OR = 1.68 (95% CI: 1.04–2.71; P = 0.034) and the result was statistically significant with P value <0.05. Even though gender was significant in the MLR analysis, it was not showing any significant association in the bivariate analysis. However, HbA1C showed significant association with DR development in univariate analysis and univariate regression analysis with OR = 0.33 (95% CI: 0.16–0.65; P = 0.0014), with the P value being < 0.01. But in MLR analysis, HbA1C had a higher likelihood of developing DR with OR = 1.01 (95% CI: 0.37–2.75; P = 0.978). However, the result did not show any significance with P > 0.05. Glycemic control showed significant association in univariate analysis (OR = 0.24 [95% CI: 0.14–0.41]; P = 0.0001) with P < 0.001 and in MLR (OR = 4.86 [95% CI: 2.21–10.66]; P = 0.0001) with P < 0.001. The variables like gender, tobacco use, glycemic control, and low HDL were independent risk factors in the development of DR in DM patients. But other variables like age, BMI, hypercholesterolemia, hyperlipidemia, hypothyroidism, and nephropathy did not show any significant association with the development of DR, as shown in Table 2.
Table 2: Distribution of comorbidities among diabetic patients with and without DR, their ORs, 95% CI and P

| Socio-demographic variables | Total patients n (%) | Cases (with DR) n (%) 192 (47.5) | Controls (without DR) n (%) 212 (52.5) | ORb | 95% CI | Pa | ORb | 95% CI | Padj | ORb | 95% CI | Padj |
|----------------------------|----------------------|-----------------------------------|--------------------------------------|-----|-------|-----|-----|-------|-------|-----|-------|-------|
| HbA1C (in %)**             |                      |                                   |                                      |     |       |     |     |       |       |     |       |       |
| ≤6.5                      | 48 (11.9)            | 12 (6.2)                          | 36 (17.0)                            | 1   | -     | -   | 1   | -     | 1     | 1   | -     | 1     |
| >6.5                      | 356 (88.1)           | 180 (93.8)                        | 176 (83.0)                           | 0.33| 0.16-0.65| 0.0014**| 1.01| 0.37-2.75| 0.978 | 0.257 | 0.001***| 0.028**|
| Poor glycemic control**   |                      |                                   |                                      |     |       |     |     |       |       |     |       |       |
| Present                   | 312 (77.8)           | 171 (89.5)                        | 141 (67.1)                           | 0.24| 0.14-0.41| 0.0001***| 4.86| 2.21-10.66| 0.0001**| 0.245 | 0.0014**| 0.116**|
| Absent                    | 89 (22.2)            | 20 (10.5)                         | 69 (32.9)                            | 1   | -     | -   | 1   | -     | 1     | 1   | -     | 1     |
| History of hypertension*  |                      |                                   |                                      |     |       |     |     |       |       |     |       |       |
| Yes                       | 323 (80.1)           | 162 (84.4)                        | 161 (76.3)                           | 0.60| 0.36-0.99| 0.044**| 1.15| 0.62-2.13| 0.650 | 0.257 | 0.001***| 0.028**|
| No                        | 80 (19.9)            | 30 (15.6)                         | 50 (23.7)                            | 1   | -     | -   | 1   | -     | 1     | 1   | -     | 1     |
| Hypcholesterolemia†       |                      |                                   |                                      |     |       |     |     |       |       |     |       |       |
| Yes                       | 332 (82.8)           | 152 (80.5)                        | 179 (84.8)                           | 1.36| 0.81-2.29| 0.245 | 0.87| 0.42-1.77| 0.695 | 0.257 | 0.001***| 0.028**|
| No                        | 69 (17.2)            | 37 (19.5)                         | 32 (15.2)                            | 1   | -     | -   | 1   | -     | 1     | 1   | -     | 1     |
| Hyperlipidemia†           |                      |                                   |                                      |     |       |     |     |       |       |     |       |       |
| Yes                       | 111 (27.5)           | 54 (28.3)                         | 57 (26.9)                            | 0.93| 0.60-1.44| 0.756 | 0.95| 0.51-1.75| 0.862 | 0.257 | 0.001***| 0.028**|
| No                        | 292 (72.5)           | 137 (71.7)                        | 155 (73.1)                           | 1   | -     | -   | 1   | -     | 1     | 1   | -     | 1     |
| Dyslipidemia†             |                      |                                   |                                      |     |       |     |     |       |       |     |       |       |
| Yes                       | 230 (56.9)           | 102 (53.1)                        | 128 (60.4)                           | 1.34| 0.90-2.00| 0.142 | 0.87| 0.54-1.40| 0.561 | 0.257 | 0.001***| 0.028**|
| No                        | 174 (43.1)           | 90 (46.9)                         | 84 (39.6)                            | 1   | -     | -   | 1   | -     | 1     | 1   | -     | 1     |
| Low HDL**                 |                      |                                   |                                      |     |       |     |     |       |       |     |       |       |
| Present                   | 284 (70.3)           | 106 (55.2)                        | 178 (84.0)                           | 4.25| 2.67-6.76| 0.0001**| 0.23| 0.14-0.38| 0.001**| 0.257 | 0.001***| 0.028**|
| Absent                    | 120 (29.7)           | 86 (44.8)                         | 34 (16.0)                            | 1   | -     | -   | 1   | -     | 1     | 1   | -     | 1     |
| Hypothyroidism†           |                      |                                   |                                      |     |       |     |     |       |       |     |       |       |
| Present                   | 52 (12.9)            | 12 (15.1)                         | 23 (10.8)                            | 1.65| 0.80-3.43| 0.177 | 1.94| 0.97-3.89| 0.62 | 0.257 | 0.001***| 0.028**|
| Absent                    | 352 (87.1)           | 163 (84.9)                        | 189 (89.2)                           | 1   | -     | -   | 1   | -     | 1     | 1   | -     | 1     |
| Nephropathy†              |                      |                                   |                                      |     |       |     |     |       |       |     |       |       |
| Present                   | 47 (11.6)            | 26 (13.5)                         | 21 (9.9)                             | 0.70| 0.38-1.29| 0.257 | 1.49| 0.73-3.05| 0.28 | 0.257 | 0.001***| 0.028**|
| Absent                    | 357 (88.4)           | 166 (86.5)                        | 191 (90.1)                           | 1   | -     | -   | 1   | -     | 1     | 1   | -     | 1     |

CI=confidence interval, DR=diabetic retinopathy, HDL=high-density lipoprotein, OR=adjusted odds ratio, ORb=odds ratio Burt. *P<0.05 statistically significant; **P<0.01 statistically very highly significant; P>0.05 statistically not significant; 95% CI Brut; 95% adjusted CI, P-value adj ‡ Burt. * P-value, P-value adj ‡ Adjusted P-value

Figure 2: Distribution and association between cases and controls among glycemic controls

Discussion

DR is a major health problem worldwide. Twenty to thirty percentage of patients were visited their family physicians with DM and its related complications. Standard algorithms are followed for the patients with DM. In our present paper, we find and discuss about the factors influencing development of DR. The influencing risk factors have to be identified and then controlled, so as to prevent the occurrence of DR in diabetic patients. In our present study, data related to age of diagnosis of DR wasn’t available, as was shown in numerous studies. In the present study, gender showed a significant association with DR in multivariate analysis. But in a study by Flores-Mena et al., gender was not found to be a significant factor in the development of DR. Similar results were obtained in several studies, which showed that gender was not a risk factor for the development of DR. Moreover, another study by Vasudevan et al. also revealed that gender was not a risk factor for the development of DR. However, in some studies, male gender was found to be an independent risk factor for the development of DR. In a study by Kajiwara et al., female gender was reported to be a prominent risk factor for DR. We found the mean age of DM patients to be 63.7 ± 11.1 years, whereas in a study conducted by Ahmed et al. in Abha, Saudi Arabia, the mean age reported was less (54.6 ± 12.3 years).

Tobacco use was identified as a protective factor. Many studies found that smoking was not a risk factor in the progression of DR. On the other hand, one study compared smokers to non-smokers with type 2 diabetes regarding DR risk and revealed that smoking decreases the risk of DR significantly, which is consistent with our results. In our present study, obesity was not
significantly related to DR, as reported in two studies that were published in the Middle East.\[5,9\] One study, however, reported a higher likelihood of DR with increased BMI,\[9\] whereas a study conducted by Sebanayagam et al.\[24\] found that BMI showed a significant inverse association with DR.

HbA1C level classification showed very high association with the progression of DR in univariate analysis, but no association in the multivariate analysis. In a study by Vasudevan et al.\[28\] HbA1C level classification was found to be a risk factor for developing DR among type II DM patients. But in a study by Flores-Mena et al.\[14\] HbA1C level was not found to be a risk factor for developing DR. In a study by Zhao et al.,\[26\] HbA1C level was reported as a significant factor in DR.

We found that DM patients with poor glycemic control were at a higher risk of developing DR. Similar results were obtained, which shows that there is a relationship between poor glycemic control and the development of DR.\[3,4,6,12,17\] A study conducted in Kuwaiti population\[9\] and also a case study by Esteves et al.\[10\] showed that poor control of blood glucose level (BGL) significantly increased the development of DR. Another study performed in the southern region of Saudi Arabia also found the link between DR and uncontrolled blood glucose versus those with good control of blood glucose.\[8\]

In our study, we found the history of Hypertension\[77\] had a significant association with the development of DR in univariate analysis, but not in multivariate analysis. A similar result was found in the Bhaktapur Retina Study in Nepal by Thapa et al.\[27\] In a study was done in northern China by Yan et al.\[28\] reported that hypertension was not a risk factor of DR. Sen et al.\[29\] mentioned in their study that hypercholesterolemia is a risk factor for the progression of DR in DM patients, whereas in our present study, hypercholesterolemia did not show any significant association with DR in both univariate and in MLR analyses. In our study, dyslipidemia was not a risk factor of retinopathy, whereas the presence of dyslipidemia was reported to be a risk factor that promoted the progression of DR in the study by Flores-Mena et al.\[14\] We found that low HDL was not a risk factor for the development of retinopathy. Similar results have been reported by Flores-Mena et al.\[14\] and Senthivel et al.\[30\] In another study by Muller et al.\[40\] HDL was found to have a positive significance with DR. Hypothyroidism was not a risk factor in the development of DR in our study, whereas in a study by Chandrakumar et al.\[32\] hypothyroidism was reported to be a prominent factor in the development of retinopathy. We found that, in our study nephropathy wasn’t a risk factor in the development of DR. Whereas diabetic nephropathy was a risk factor for the progression of DR.\[33\] Furthermore, some other studies revealed that neuropathy and nephropathy were the associated factors of retinopathy.\[3,5,12,18\] In our present study, we did not assess the medications that were used to control diabetes, unlike other studies which found that insulin use increases the risk of having DR.\[39,10\] A limitation of this study is that no data are available related to duration of diabetes.

### Conclusion

Our study findings showed male gender, tobacco consumption, poor glycemic control, and low HDL to be independently associated with the development of vision-threatening disease (DR). By doing regular check-up for DR, DM patients could maintain their risk factors as normal and free from DR or retain their DR stage in the same stage or to prolong DR among DM patients.

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### Conflicts of interest

There are no conflicts of interest.

### Key Messages

1. Diabetes patients have to check their blood glucose level once in 3 months with their family physician and control it within the normal range.
2. Diabetes patients should have to check periodically with a primary care physician for the risk factors of DR. Then only they have to control or stop the progression of diabetic retinopathy.
3. Once DM patients came to know they are having DR then they have to check their eyes once in 6 months to control its severity, to avoid it's progression to the next stage and to prevent from loss of eye sight.
4. Diabetes mellitus patients should avoid smoking.

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