A study of retinopathy analysis in type 2 diabetes patients in Chinese population

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Abstract: In this investigation, the risk factor that arises from diabetic retinopathy was assessed in type 2 diabetes patients. The study is based on a 5-year community-based program, which comprises of 750 participants of the Chinese population. The study comprises general eye examinations, retinopathy assessment, anthropometric and laboratory measurements. The data thus obtained was statistically analyzed and the factors related to Diabetic retinopathy (DR) were deduced. Statistical analysis observed that retinopathy is prone to diabetes patients with high blood pressure and hyperglycemia in Chinese patients with type 2 diabetes. To conclude, the occurrence of DR was associated in patients with baseline hyperglycemia and high blood pressure. In addition, the DR regression was mostly related to lower baseline glucose and lower serum triglyceride levels among the type 2 diabetes patients in the studied Chinese population.

Keywords: Diabetic retinopathy, Chinese population, type 2 diabetes, regression.

INTRODUCTION

Diabetic retinopathy (DR) is an eye disease caused by the damage to the retina due to diabetes. It is usually a common complication of diabetes mellitus that can ultimately lead to blindness (Tapp *et al., 2003*). There are no early signs and warning of this disease. It affects up to 80 % of patients which is associated with more than 20 years of diabetes (Kertes and Johnson 2007). The longer a person has diabetes, the higher the chance of developing DR. Even though, there are many treatments for DR, it is considered as the most common cause of blindness in some Western Countries which includes USA, Canada, England and France (Mitchell *et al*., 2015; Wong *et al*. 2008). Majority of the DR cases could be lessen if they given proper treatment and given proper assessment of the eyes. The cause of DR is due to the damage of neuronal cell of the retina and blood vessels. The initial stage of DR includes narrowing of the retinal arteries and reduction in the retinal blood flow (Wong *et al*., 2008). DR is also the cause of loss of vision in adults with ages 21–70 years and it is estimated that around 95 million people have signs and symptoms of DR based on a report in 2010 (Cheun *et al*., 2010; Bourne *et al*., 2013). Additionally, the rate of DR is rising because of the rise of diabetic patients (He *et al*. 2013). The only way to control the retinal complication in diabetes patients is to prevent the disease from happening (Thomas *et al*., 2015; Knudsen *et al*., 2006). Hence, it is important to identify the factors and parameters that are associated with DR. In this study, the participants were allowed to control the DR progression by controlling their blood glucose. Furthermore, the patients were permitted to accept only systematic treatments for hypertension, microcirculation, high blood glucose levels and hyperlipidemia. The present study is based on a 5-year community that comprises of 750 participants of the Chinese population. The aim of the study is to assess and identify the important factors associated with DR and thus preventing the blindness in diabetic patients. Our investigation also aims at the determination of the onset of DR and its regression rate in the Chinese population having diabetes. By studying these factors which is related to the regression of DR, there is a possibility of slowing down the progression of the diseases as well as reversing the existing disease. Thus preventing a late stage DR. The reason for the regression of DR in this study was observed and suggests that patients with early of DR have the option of slowing down the retinopathy progression. The study will give a new strategy on the risk factors prevailing in DR patients associated with diabetes in the Chinese population.

MATERIALS AND METHODS

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Setting and participants

The population assessed for DR in this investigation is Foshan, which is located in the Central Part of Guangdong province of the PR China. During the examination and monitoring of the participants, due care was taken and the participants were permitted to take necessary medicines to control systemic diseases. The

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participants with abnormally high blood sugar were permitted to take anti-hyperglycemia drugs such as sulfonylureas, metformin, insulin etc. Furthermore, the participants were advised to restrict on diet chart, control cigarette smoking, physical exercise etc. to control hyperglycemia. The blood glucose levels of the patients were checked once in every week by capillary blood glucose determination method. The hemoglobin levels (HbA1c) of the patients were also measured only one time per year. In addition, the participants who had hypertension were also permitted to take anti-hypertension drugs including ACEI, CCBs etc. The volunteers having excess lipids in the blood (hyperlipemia) were also allowed to take drugs for lowering the lipid profile. Furthermore, the volunteers with invasive treatment during the follow-up were not considered for the study. And only the patients without apparent DR, moderate and severe DR without persistent action were included. The present study criteria are based on the World Health Organization (WHO) criteria (Alberti and Zimmet, 1998) and the patients with diabetes were above 21 years of age without any record of ophthalmologic surgery. Additionally, the patients' consent was taken for physical examination and signatures were taken for the voluntary consent form. However, the participant's who were suffering from other systemic diseases such as cancer, heart disease and severe eye diseases other than diabetes were excluded in the study.

Measurements and general examinations

Initially, the information of the volunteers was acquired from the local health center database which includes their age, sex, duration, onset details, educational qualification, and ophthalmological episodes. In addition, the weight and height of the patients along with the systolic (the top number) and diastolic (the bottom number) blood pressures were measured using an electronic sphygmomanometer on the left arm in the supine position. The period of the diabetes was taken as the gap amid the baseline examination and detection of diabetes. In this study, hypertension is described as systolic (the top number) ≥140 mmHg (mercury) and diastolic (the bottom number) ≥90 mmHg. In addition, BMI was measured according to weight/height in kg/m^2 and those participants whose BMI≥28 is considered as obsessed or with obesity (Wu 2006). The Blood test that measures the fatty substances such as total cholesterol (blood cholesterol), triglycerides test, serum creatinine test, micro albuminuria and glycated hemoglobin (HbA_{1c}) was carried out. Blood cholesterol, triglycerides and serum creatinine test was done using an enzymatic assay. While the presence of excessive blood plasma protein (micro albuminuria) was examined by nephelometry, the glycated hemoglobin (HbA_{1c}) was determined using High-performance liquid chromatography (HPLC) techniques. Hyperlipidemia was declared if the serum triglyceride level was greater than or equivalent to 1.7mmol/L. Hypercholesterolemia was declared if the cholesterol levels were greater than or equivalent to 5.2mmol/L. In addition, the participants having ≥30mg/L of micro albuminuria levels and ≥104 mmol/L were considered as suffering from renal dysfunction. The HbA_{1c} of each of the patients was measured once per year during the five year study period and the average of HbA1c was calculated for the five years study period.

Retinopathy assessment analysis

The enrolled participants were conducted for retinopathy assessment taking 2010 as the baseline and 2014 as the final survey. General eye and visual acuity testing was performed based on the Early Treatment Diabetic Retinopathy Study table. The examination was carried out for eyelid, iris, conjunctiva, cornea and lens using a slit-lamp microscope. The participants were examined and screened for DR based on the procedure followed by Peng *et al*. (2011). Initially, the vitreous and fundus of the patients were examined using an ophthalmoscope. Photographs were taken and recorded for the posterior pole using a non-mydriatic funduscopic camera. In addition, digital retinographs were taken based on the protocol described by Gibbins *et al*. (1998) and two retinographs at 45˚ were obtained per eye by way of one centered on the macula while the other to the nasal of the optic disk (Gibbins *et al*., 1998). Furthermore, optical coherence tomography (OCT) and fluorescein angiography (FAG) was carried out for those patients who has inferred DR based on the evaluations. The evaluations were carried out to substantiate the detection and severity of the DR. The DR grades of the patients were classified based on the ICDR and DMED Severity Scale that is accepted universally (Wilkinson *et al*., 2003). The classification of DR grades was made based on the clinical and physical observations conducted by the ophthalmologist of our hospital. The grade chart of the DR is listed in table 1.

In the current investigation, DR incidence was assessed in two different outcomes mainly from zero grade to grade 1–4 in any one of the eye or both. While the other as the decrease in the severity of DR (1-4 grades to zero) in any one of the eyes or both without further DR.

STATISTICAL ANALYSIS

Statistical analysis was carried out using SPSS 17.0 (SPSS, IBM, U.K.) and Microsoft Excel 2007 (Microsoft Corporation, USA). For the categorical data with continuous variables, the baseline characteristics are represented with the means ± standard deviation and for the variables with normal distribution, the t-test was carried out and the mean values were compared between the groups. The categorical data with continuous variables were compared with the Chi-square test. In addition, the

univariate logistic was also carried out for the variables whose value is less than 0.5, which were further considered for the multiple logistic regression analysis. The multiple regression analysis was carried out to understand the potential and probable risk factors from the observed parameters that are associated with the DR onset and DR regression. The studied or the observed parameters include the age of DR onset, diabetes duration, blood pressure, blood glucose level etc which is presented in tables 2 and 3. The $p<0.05$ (two-tailed) was considered as statistically significant.

RESULTS

In the present study, 750 participants having diabetes were enrolled for the DR assessment studies. The assessment studies observed that 610 patients were experiencing high blood pressure. In addition, these patients were mostly under prescription with angiotensin inhibitors treatments to stabilize the hypertension. The dosage varied from patient to patient. Moreover, 315 participants developed DR in any one of their eye and the incidence of DR in the follow up period was analyzed. The remaining 435 participants already developed DR in any one of the eye were analyzed for its regression.

Risk factors

There were 315 participants at the time of baseline survey in the year 2010 which were free from Diabetic Retinopathy. Among them, 137 (43%) were male and 178 female (57%). The oldest participant was an 88 years old male and the youngest a 21-year-old boy. A total of 265 participants (84%) were more than 60 years old and 50 participants (16%) were less than 60 years of age. Interestingly, in 10 of the assessed participants, diabetes was thought to have occurred or diagnosed with the last year of the study period (2014). While the longest diagnosed period was 27 years from a 78 year old male patient. Out of the 148 patients with DR development, a total of 75 participants (34%) were diagnosed with diabetes for more than 10 years. In addition, values of the micro albuminuria of all the participants were found to be less than 27 mg/L. The details of the information about the DR-free volunteers are presented in table 2. After 5 years of the study period, 148 patients were diagnosed with DR development in either one of the eyes with an incidence rate of 47%. About 56% (85 patients) were diagnosed with DR grade-1 incidence, 21% (32 patients) with DR grade-2, 11% (19 patients) with DR grade-3 and 3% (5 patients) with DR grade-4. In addition, the patients who had developed DR in both the eyes were 92% of the population size of 135. Interestingly, it was observed that the patients with hypertension, high level ofHbA1c baseline and average HbA1c level with above 60 years of age were developing DR (table 2). However, from the statistical analysis using the univariate logistic regression, it is also revealed that hypertension (Odds ratio = 1.64, CI @ 95% = 1.22–2.54, p=0.02) and high baseline HbA1c (Odds ratio =1.12, CI @ 95% = 0.96–1.21, p=0.03) were primary factors. In fact, these factors are independent variables that lead to the incidence of DR.

Factors leading to the regression of DR

A total of 435 participants having DR at the baseline entry were studied. 176 participants (40%) were male and the range of the ages was from a 26 year old male to an 89 year old female. The duration of diabetes ranges from 1 year to 28 years and around 40% of the patients had diabetes for more than 10 years. The presence of micro albuminuria (excessive protein in the urine) values was also found to be less than 28 mg/L in all the participants. The detailed characteristics of the patients with and without DR regression are presented in table 3.

In the present study, 96 patients observed DR regression in both the eyes out of the total of 103. While 7 patients were observed with DR regression in either of the eyes with no further deterioration. Additionally, the severity of the DR grade was further regressed to DR grade-0 during the five year study period. The overall DR regression rate in the studied population was found to be 23%. While the DR regression rate from DR grade-1 to grade-0 was found to be highest with 70% and 25% from DR grade-2 to grade-0. However, there was no occurrence of DR regression from patients with grade 3 or grade 4 that exhibited a full DR regression to grade- 0.The statistical analysis also revealed that DR regression is associated with normal levels of serum triglyceride, lower baseline HbA1c, low average HbA1c with short duration of diabetes (table 3). The statistical analysis carried out by means of the univariate logistic regression also revealed that lower baseline HbAlc (Odds ratio =0.51, CI @ 95% = 0.41–0.61, p<0.01) and low level of serum triglyceride (Odds ratio =0.69, CI @ 95% = 0.57–0.87, p=0.03) were also two independent factors contributing to the regression of DR regression.

DISCUSSION

The present assessment studies imply that high glucose and hypertension are two major risk factors for DR in the studied population. The present findings are also in agreement with those of the previous reports by Manaviat *et al*. (2008) where the workers also conducted an assessment study on other populations (Manaviat *et al*., 2008). The retinal damage caused by the pathogenesis of high blood pressure and glucose level remains indistinct in this investigation. However, there were reports which suggest that the chronic hyperglycemia and hypertension has led to oxidative injury, microthrombi formation and leukostasis of cell adhesion. Additionally, the activation of cytokines such as insulin-like growth factor-1, tumor necrosis factor (TNF) and vascular endothelial growth factor (VEGF) which is responsible for retinal damage was also observed (Thomas *et al*., 2012 and Romero-Aroca *et al*., 2011).

Table 1: DR Grade chart

S. No.	DR Grade	DR incidence
1	Grade 0	No obvious DR
2	Grade 1	Mild non-proliferative DR
3	Grade 2	Moderate non-proliferative DR
4	Grade 3	Severe non-proliferative DR
5	Grade 4	Proliferative retinopathy9

However, there was no evidence of DR onset associated with the duration of diabetes. The inconsistency may be because the onset of the diabetes is usually unknown and disease could have developed in the patient long before (Stratton *et al*., 2001; Varma *et al*., 2000). In comparison to the incidence of DR by various workers from different populations in many countries, the DR incidence varies from 5% to 45% that may be because of the food habits, environmental factors and racial difference (Xu *et al*., 2014; Jin *et al*., 2014). In our study, the cumulative incidence of DR was 44% which is in agreement with the published reports by Manaviat *et al.* (2008). Additionally, various workers have reported that the Asian population is more prone to high blood glucose levels and a higher chance of developing DR (Bao *et al*., 2010). However, the duration of diabetes is not an independent factor related to the onset of DR in the present study (Wells *et al*., 2015).

In spite of the high DR incidence, the regression of the cases was found to be relatively common among the patients with well-controlled glucose levels and DR with mild baseline. Interestingly, Zavrelova *et al.* (2011) and White *et al.* (2011) also observed the spontaneous setback of DR (Zavrelova *et al*., 2011 and White *et al*., 2011). However, Bressler *et al*. (2015) also observed that association of DR is related to certain systemic factor (Bressler *et al*., 2015). The DR regression rate in the present study was found to be 21% which is quite high compared to other reports (Han *et al*., 2004). The higher regression rate may be because of the systemic situation of the studied participants with lesser complications of the disease. The participants in the present study did not have any systemic disease such as cancer, heart disease and severe eye diseases, whereas the other reports with low DR regression rate include those patients with circulation and cardiac problems (He *et al*., 2014). The mean baseline HbA1c of the studied participants was comparatively low compared to other existing reports (table 3). It is also observed that the DR regression is associated with the maintenance of euglycemia. Additionally, the strict control of the blood glucose might be an important factor that leads to the lesser worsening of the eyes. Hence causing a higher DR regression rate. Another probable reason for the high DR regression rate may be because of the anti-hypertension drugs prescribed to the patients to control hypertension and hence improve the microcirculation. Interestingly, Zheng *et al*. (2009) also reported on the effectiveness of ACEI therapy in supporting higher DR regression rate (Zheng *et al*., 2009). The present study also observed that DR regression occurs only in participants with early retinopathy.

The study indicated that the lower level of the serum triglyceride is also a general factor which is an individual factor causing the DR regression. These findings are also consistent with the other reports described by Jin *et al*. (2014). Additionally, there are various reports that described the association of the level of serum lipid with the sternness of hard exudates (Gordon *et al*., 1991).

Table 2: Clinical characteristics of the participants with and without DR development during the five year study period

	Total	DR development	No DR development	Statistical value	P value
Number of participants	315	148 (47)	167 (53)		
Age (years)	65±11.21	66±12.65	63±11.34	2.41	0.02
Age<60	50 (16%)	18 (6%)	26 (8%)	3.87	0.03
60<age<70	113 (36%)	51 (16%)	66 (21%)		
70<age<80	133 (42%)	69 (22%)	66 (21%)		
Age>80	19 (6%)	13 (4%)	6 (2%)		
Male gender	137 (43%)	62 (45%)	75 (55%)	0.27	0.51
Diabetes onset age (years)	54.06±12.19	55.41±14.16	51.72±12.15	1.89	0.03
Diabetes duration (years)	10±7.18	10±7.76	10.±7.89	-0.39	0.57
Duration<10	155 (49%)	73 (49%)	82 (49%)	0.02	0.87
10<duration<20	99 (31%)	45 (30%)	54 (32%)		
20<duration<30	58 (18%)	28 (19%)	30 (18%)		
Duration>30	3 (1%)	2 (1%)	1 (1%)		
Obesity	33 (10%)	18 (12%)	15 (9%)	0.81	0.29
High blood pressure	130 (41%)	72 (49%)	58 (35%)	4.12	0.02
High serum creatinine	15 (5%)	8 (5%)	7 (4%)	0.61	0.39
Hyperlipidemia	112 (36%)	51 (34%)	61 (37%)	0.11	0.67
Hypercholesterolemia	198 (63%)	95 (64%)	103 (62%)	0.18	0.64
Baseline HbA1c (%)	7.61±1.98	7.78±2.12	7.34±2.45	2.12	0.01
Average HbA1c (%)	6.71± 1.76	6.77± 1.51	6.51±1.72	-8.87	0.01

Table 3: Clinical characteristics of the participants with and without DR regression during the five year study period

	Total	DR regression	No DR regression	Statistical value	P value
Number of participants	435	103	332		
Age (years)	67±11.34	68±12.14	68±10.14	-1.24	0.12
Age<60	49(11%)	20 (19%)	29 (9%)	1.36	0.21
60<age<70	129 (30%)	23 (22%)	106 (32%)		
70<age<80	205 (47%)	49 (48%)	156 (47%)		
Age>80	52 (12%)	9 (9%)	43 (13%)		
Male gender	184 (42%)	43 (42%)	141 (42%)	0.07	0.81
Diabetes onset age (years)	55.25±12.34	56.34±14.73	56.21±12.12	0.72	0.48
Diabetes duration (years)	10±7.12	10±7.81	11±8.91	-1.89	0.02
Duration<10	201 (46%)	57 (55%)	144 (43%)	4.42	0.03
10<duration<20	144 (33%)	27 (26%)	117 (35%)		
20<duration<30	97 (22%)	14 (14%)	83 (25%)		
Duration>30	4 (1%)	2 (2%)	2 (1%)		
Obesity	85 (20%)	22 (21%)	63 (19%)	0.03	0.79
High blood pressure	200 (46%)	49 (48%)	151 (45%)	0.03	0.82
High serum creatinine	11 (3%)	1 (1%)	10 (3%)	2.81	0.08
Hyperlipidemia	179 (41%)	31 (30%)	148 (45%)	3.72	0.03
Hypercholesterolemia	287 (66%)	63 (61%)	224 (67%)	0.58	0.39
Baseline HbA1c (%)	7.14±2.11	5.42±1.23	7.49±1.89	-9.76	<0.01
Average HbA1c (%)	6.45±1.21	5.87±1.21	7.13±1.02	-9.67	<0.01

Furthermore, it has also been reported that the association of hard exudates regression with a lower level of lipid therapy were able to decrease the need for laser photocoagulation (Hellstedt *et al*., 1996). The participants were taken due care and given proper awareness on controlling the blood glucose levels even after the enrollment. The study also revealed that there was a gradual HbA1c decreased through the clinical examination episode. The results illustrated that the baseline HbA1c were more related to DR development and DR regression among the patients instead of average HbA1c during the 5-year follow-up. The relation with the baseline HbA1c might be because of a phenomenon called the metabolic memory which was earlier described by Roy *et al* (1990).

CONCLUSION

To conclude, the authors would like to highlight that during the 5 year study period, the occurrence of DR was associated in patients with high blood sugar and hypertension. In addition, the DR regression was generally related to low glucose level and lipid profile in the studied Chinese population. However, the study has certain boundaries as the studied residents are restricted to a single community of the Chinese Population.

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