Research Square

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The related risk factors of diabetic retinopathy in elderly patients with Type 2 diabetes mellitus: A cohort study

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Abstract

Background: Diabetic retinopathy (DR) caused by small vessel disease was the main cause of blindness in person with diabetes, and it mainly occurred in patients with Type 2 diabetes mellitus (T2DM). Taiwan was one of the Asian countries with the highest prevalence rate of DR, there were only few studies for the risk of DR in patients with T2DM in Taiwan. According to some studies have shown DR was a major cause of blindness on elderly both in developed and other developing countries. The purpose was to investigate the related risk factors of DR in elderly patients with T2DM.

Methods: During July 2010 to December 2017, 4010 T2DM patients without DR were preselected for this study, but 792 patients completed the continuously follow-up evaluation. Patients were invited to have an outpatient visit at least every three months, and they were asked to fill out a brief questionnaire and collect their blood samples. Additionally, statistical methods used independent sample T-test, Chi-square tests and logistic regression in univariate analysis to analyze the relationships between onset DR and each related factor; and finally the optimal multivariate logistic regression model would be determined by stepwise model selection.

Results: Of the 792 effective samples, 611 patients (77.1%) progressed to DR and 181 patients (22.9%) did not get DR during the follow-up period. According to the results, the significant factors were women (OR, 2.20; 95%CI, 1.52-3.17), longer diabetic duration (OR, 1.05; 95% CI, 1.03-1.08), family history of diabetes (OR, 1.55; 95% CI: 1.09-2.21), higher concentration glycated hemoglobin (HbA1c) (OR, 1.27; 95% CI: 1.12-1.44), higher mean low density lipoprotein cholesterol (LDL-c) (OR, 1.01; 95% CI: 1.00-1.01), and chewing betel nut (OR, 2.85; 95% CI: 1.41-5.77).

Conclusions: This prospective cohort study showed that gender, behavior of chewing betel nut, diabetic duration, family history of diabetes, HbA1c, and LDL-c, were important factors for the development of DR in elderly patients with T2DM. It suggested that those patients should well control their HbA1c and LDL-c and quit chewing betel nut to prevent from DR, especially for female patients with family history of diabetes and longer duration of diabetes.

Background

Diabetes was a common chronic metabolic disorder lifelong disease. Patient with diabetes must control and manage their blood glucose, blood pressure and lipid by changing their lifestyle and dietary habits to prevent from large or small blood vessels, and diabetic neuropathy. If not, their disease progression could develop to deterioration such as cerebrovascular, heart coronary artery and other diseases including diabetic retinopathy (DR), kidney disease, feet ulcer and other complications that pose a major threat to the worsen of symptoms.[1,2] In 2015, the WHO published that the prevalence of diabetes was 8.8%. In 2017, statistics from the International Diabetes Federation (IDF) also showed that there were 425 million people suffering from diabetes worldwide and predicted to reach 629 million in 2045 for patient's age from 20 to 79. This means 1 in 11 adults experiences diabetes; and among that numbers, 87%-91% has

Type 2 diabetes mellitus (T2DM). In the meantime, 5 million people worldwide will die from diabetes, which shows one death at every six seconds. Diabetes accounted for 14.5% of all causes of death in the world, and it was higher than the total number of deaths from infectious diseases in 2013.[3] According to Taiwan's survey during 2013 to 2015, the prevalence rate of diabetes in patients over 18 years of age was 11.8%, which was higher than the global prevalence of diabetes. It was also reported that there were about 2.275 million people with diabetes in Taiwan, and was increasing by the rate of 25,000 patients every year.[4] As a result, diabetes has become Taiwan's top five leading causes of death since 1987.[5] The complications of diabetes not only affect the health of people but also lead to the medical burden. Therefore, it is very important to explore the risk factors of diabetic complications that bring the significant impact on patients with diabetes.

In 2011, the prevalence rate of diabetes in the population aged over 20 was about 8% in Taiwan and it was estimated that there are more than 1.4 million patients with diabetes. The medical expenses for diabetes in Taiwan on National Health Insurance Administration were about 18.4 billion Taiwan dollars a year, accounting for about 4% of the annual expenditure. Many complications and diseased organs were due to diabetes, including kidney disease, heart disease, stroke, diabetic retinopathy, vascular, etc. The cost of hemodialysis was about 30.8 billion Taiwan dollars per year, which was the highest among others. Moreover, the proportion of hemodialysis patients with kidney disease caused by diabetes reached 40%.[6] As a result, the medical expenses associated with diabetes and diabetes complications are essential parts of the medical expenses. It is also significantly increase the medical burden worldwide. The global healthcare expenditure on diabetes patients had reached to $376 billion US dollars per year, which accounted for 12% of the world's total medical expenses in 2010.[7] The medical cost of patients with diabetes with vascular complications was four times than that of patients with diabetes without vascular complications[8], DR caused by small vessel disease was the main cause of blindness in person with diabetes, and it mainly occurred in patients with T2DM.[9] Therefore, diabetes complication imposes an increasing economic burden on national health care systems worldwide. With the diabetes prevalence, death attributable to diabetes and medical burden continue to rise; it is very important to manage the health condition of patients with diabetes.

DR accounted for 5% of all blindness in the world; and it was a major cause of blindness on elderly both in developed countries (such as the United States and United Kingdom) and other developing countries (such as Taiwan).[10–12] DR will lead to the vision loss that will seriously affect the quality of life for patient and their families. A study pointed out that 1.9% of DR lead to blindness and 10.2% of DR leads to visual impairment in the world in 2015.[13] The related research reported that there were 32.4 million blind people and 191 million people living with impairment in 2010, and DR accounted for 2.6% of people who were blind. The number of visual impairment caused by DR increased from 1.858 million in 1990 to 3.074 million in 2010.[14]

The prevalence rate of DR in Asia-Pacific was 23%; it was 12.1% in Hong Kong, 25.4% in Singapore and 15.8% in Korea.[15] Comparing to other Asia countries, the prevalence rates of DR in Taiwan reached to

31.1%.[16] Many studies have indicated that diabetic duration or treatment methods would affect the risk of DR.[12,17–19] Some published literatures also reported that well maintained blood glucose, blood pressure and cholesterol levels in the normal level could reduce the risk of DR, and prevent from vascular complications which lead to visual impairment; it was also helpful in delaying DR from progressing into deterioration.[20–22] But the prevalence rate of DR was still high in Asia due to the increasing incidence of diabetes every year. Although Taiwan was one of the Asian countries with the highest prevalence rate of DR, there were only few studies for the risk of DR in patients with T2DM in Taiwan. Therefore, the main purpose of this study is to discover the related factors that affect the risk of DR in patients with T2DM. Furthermore, the other aim is to improve the consciousness and knowledge of the risk of DR in patients with T2DM as well as to reduce the incidence rates of DR in patients with T2DM in Taiwan.

Methods

Subjects

From July 2010 to December 2017, 4010 T2DM patients without DR were preselected for this study in Lee's Endocrinology Clinic; among them, 792 valid samples were in accordance with the study sample inclusion and exclusion criteria and received continuously follow-up. Patients were invited to have an outpatient visit at least every three months, and an ophthalmologist performed dilated fundus examination to evaluate and determine whether the patients with T2DM progressed to DR. The study samples were included in the following conditions: (I) T2DM patients were diagnosed without DR (II) patients were over 60 years of age (III) patients performed regular visit clinic for diabetes checkups and dilated fundus examinations at least every three months. Exclusion criteria of study samples were as the following conditions: (I) patients with monocular or bilateral blindness before or during the study, (II) patients with glaucoma not caused by diabetic diseases, or (III) those who were losing to follow-up or unwilling to be involved during this study.

Materials And Methods

All participants in each outpatient visit were asked to fill out a brief questionnaire and collect their blood samples to check or access glycated hemoglobin (HbA1c), fasting plasma glucose, triglyceride (TG), total cholesterol (CHOL-T), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c) and the estimated glomerular filtration rate (eGFR), usually four or five times a year. The brief questionnaire was for obtaining patient’s information including gender, education level, body mass index, diabetic duration, family history of diabetes and health habits. Education level of participants was defined as no qualifications, elementary school, and junior high school or higher. Body mass index (BMI) was measured as weight divided by height squared (kg/m^2). Diabetic duration of T2DM patients with DR defined as the time (years) was from the onset time of diabetes to the time of first diagnosis at each stage of DR progression, and diabetic duration of T2DM patients without DR defined as the time (years) was from the onset time of diabetes to the latest time for dilated fundus examinations. Health habits of

participants were included the behavior of smoking, drinking, chewing betel nut and regular exercise. Smoking behavior was defined as smoking any type of cigarette at least once a day for a period of 6 months or longer. Drinking behavior was meant as drinking any type of alcoholic beverage at least three times a week for a period of 6 months or longer. Behavior of chewing betel nut was defined as chewing areca nut at least once a day for a period of 6 months or longer. Regular exercise behavior was meant as exercising regularly at least three times a week for a period of 6 months or longer. Blood pressure (systolic blood pressure and diastolic blood pressure) was taken by digital automatic blood pressure monitor with the participant seated after resting for 5 minutes. The levels of creatinine, fasting plasma glucose, TG, CHOL-T, and HDL-c were measured on an analyzer with enzymatic assay; and HbA1c was measured on an analyzer using a High-performance Liquid Chromatography. The eGFR could be measured by the level of creatinine in the blood and use the result in a formula to calculate a number that reflected how well the kidneys was functioning. Also, LDL-c could be calculated by a formula including TG, CHOL-T, and HDL-c.

Dilated fundus examination procedure

In order to obtain a better view of the fundus of the eye, dilated fundus examination included eyesight test, automatic optometric examination, and air puff test; and it was a diagnostic procedure that employs the use of mydriatic eye drops (such as Mydrin-P) to dilate or enlarge the pupil. The value of intraocular pressure must be reported as normal before dilated eye exam. The ophthalmologist used the mydriatic eye drops, and delivered the eye drop every 5 minutes for three times. After 30 minutes, the patient's pupil would stay open with size naturally enlarged then the ophthalmologist could use ophthalmoscopy to view the eye's interior, allowing assessment of the retina, blood vessels, optic nerve head, and other features. It would allow ophthalmologists to diagnose and monitor the degree of DR in more details after obtaining digital images from all participants.

Statistical analysis

Participant's characteristics were described by absolute and relative frequency for categorical variables, means and standard deviation for continuous variables. In inference statistic methods, independent sample T-test was used to analyze the difference of the mean for continuous data in patients with and without DR; and Chi-square tests was used to analyze the difference in the proportion of categorical variables between the patients with and without DR. Logistic regression methods applied to test the associations between onset DR and each related factors in univariate analysis. Finally, the significant factors in each statistic testing would be considered into the model, and the optimal multivariate logistic regression model would be determined by stepwise model selection. Those results were reported as odds ratios (OR) with a 95% confidence interval. A p-value < 0.05 was considered to be statistically significant. Statistical analysis was performed using IBM SPSS Statistics 24.

Results

792 patients with T2DM were effectively enrolled in the study; their average age was 67.85 (SD = 6.53). During the follow-up period, 611 patients (77.15%) progressed to DR but 181 patients (22.85%) did not. In this study, there were 339 males (42.80%) and 453 females (57.20%), 493 patients (62.25%) were with family history of diabetes and 299 patients (37.75%) without family history of diabetes, 453 patients (57.20%) had regularly exercise behavior and 339 patients (42.80%) did not, 189 (23.86%) patients were with smoking behavior and 603 patients (76.14%) were without smoking behavior, 149 patients (18.81%) were with drinking behavior and 643 patients (81.19%) were without, and 79 patients (10.00%) were with the behavior of chewing betel nut and 713 patients (90.00%) were without.

According to the results in Table 1, the significant predictive factors for DR in elderly patients with T2DM included gender, family history of diabetes and chewing betel nut behavior. The 81.02% retinopathy rate of female patients was higher than that of male patients at 71.98% ($\chi2 = 8.99$, $P = 0.003$). The retinopathy rate of patients with family history of diabetes was at 81.14%, which was higher than the 70.57% ($\chi2 = 11.79$, $P = 0.001$) of those with no family history of diabetes. The rate of DR of patients with T2DM with and without chewing betel nut behavior was 86.08% versus 76.16%, respectively ($\chi2 = 3.97$, $P = 0.046$). Additionally, univariate logistic regression analysis indicated that women (OR: 1.66, 95% CI: 1.19–2.32), family history of diabetes (OR: 1.79, 95%CI: 1.28–2.51) and behavior of chewing betel nut (OR: 1.93, 95% CI: 1.00-3.74) were associated with the presence of DR. However, there was no significant association between education level, smoking behavior, drinking behavior, regular exercise behavior and the development of DR.

In Table 2, the factors, the diabetic duration, HbA1c, TG, CHOL-T and LDL-c, were associated with the development of DR in elderly patients with T2DM. The average of diabetic duration of T2DM patients with DR, 19.18 (SD = 8.22) years, was higher than the average of diabetic duration of T2DM patients without DR, 15.79 (SD = 8.24) years ($t=-4.86$; $P < 0.001$). The mean concentration of HbA1c of patients with DR, 8.25 (SD = 1.68) % on average, was higher than that of patients without DR, 7.66 (SD = 1.47) % on average ($t=-4.61$; $P < 0.001$). The mean concentration of TG of patients with DR was 1.56 (SD = 0.87) mmol/L, which was higher than that of patients without DR, 1.45(SD = 0.64) mmol/L ($t=-2.39$; $P = 0.017$). The mean concentration of CHOL-T of patients with DR, 2.13 (SD = 0.43) mmol/L, was higher than that of patients without DR, 2.00 (SD = 0.33) mmol/L ($t=-4.44$; $P < 0.001$). The mean concentration of LDL-c of patients with DR, 1.12(SD = 0.34) mmol/L, was higher than that of patients without DR, 1.04 (SD = 0.27) mmol/L ($t=-3.26$; $P = 0.001$). Besides, univariate logistic regression analysis indicated that diabetic duration (OR:1.06, 95% CI: 1.03–1.08), HbA1c (OR:1.29, 95%CI:1.14–1.45), TG (OR:1.01, 95%CI:1.00-1.01), CHOL-T (OR :1.01, 95%CI:1.00-1.01) and LDL-c (OR:1.01, 95%CI:1.00-1.01) were associated with the presence of DR. However, factors such as BMI, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, HDL-c and eGFR were not significantly associated with the development of DR in elderly patients with T2DM.

Integrating the results from Table 1 and Table 2, the factors including gender, behavior of chewing betel nut, diabetic duration, family history of diabetes, HbA1c, TG, CHOL-T and LDL-c were associated with the development of DR. According to the multivariate logistic regression analysis by stepwise model

selection, we found that the significant factors associated with the occurrence of DR in elderly patients with T2DM, retained in the optima model, were women (OR, 2.20; 95%CI, 1.52–3.17), longer diabetic duration (OR, 1.05; 95% CI, 1.03–1.08), family history of diabetes (OR, 1.55; 95% CI: 1.09–2.21), higher HbA1c (OR, 1.27; 95% CI: 1.12–1.44), higher LDL-c (OR, 1.01; 95% CI: 1.00-1.01), and behavior of chewing betel nut (OR, 2.85; 95% CI: 1.41–5.77), as showed in Table 3.

Discussion

This study found that the factors such as gender, behavior of chewing betel nut, diabetic duration, family history of diabetes, HbA1c, and LDL-c, were important predictors of DR in elderly patients with T2DM. The risk of DR in female patients was higher than that of men. The longer duration of diabetes was the higher risk of retinopathy would be. The risk of retinopathy of patients with diabetic family history was higher than that of patients without family history. The patients with behavior of chewing betel nut had higher risk of developing retinopathy. The patients with higher HbA1c posed higher risk of developing retinopathy. The patients with higher LDL-c were associated with higher risk of developing retinopathy.

For the gender factors, Lopez et al. (2017) determined that retinopathy in women are more common related to retinopathy in elderly patients with T2DM.[23] Another retrospective study also found that women were more likely to have retinopathy than men[24], the results of which matched the results of this study. The estrogen production could regulate ocular blood flow to protect the retina; and its antioxidant effects were the primary protective effect on the lens. When women aged over 50, the concentration of estrogen would decrease year by year, and gradually lost the protect function from estrogen.[25–26] The average age of women in our study was over 65 years old. These could be the reasons to explain that risk of DR was higher in females.

In a recent study of relationships between diabetic duration and risk of DR in patients with T2DM, the result showed that the prevalence of retinopathy was 1.1% at the first time of diagnosis, 6.6% for diabetes duration less than 5 years, 12.0% for diabetic duration between 5 to 10 years, 24.0% for diabetic duration between 10 to 15 years, 39.9% for diabetic duration between 15 to 20 years, and 52.7% for diabetic duration over 20 years. Therefore, the prevalence of DR in patients would rise substantially when the patient's diabetic durations were over 10 years.[27] Some studies also found that the longer duration of diabetes, the higher chance of retinopathy appeared; with impact on the risk of DR.[17,24,28] The result of those studies were corresponding to our study. Therefore, well controlled earlier could prevent and delay the progression of DR in patients with diabetes.

Lopez, et al., (2017) found that patients with a family history of diabetes had a higher proportion of developing DR; and the number of patients with a family history of diabetes was about 63.4%.[23] The genetic inheritance and life style had a great influence on the induction of T2DM.[29] Therefore, T2DM patients with family history of diabetes should definitely manage their lifestyle and control diabetes. Keeping the blood glucose level balanced was one of the most important steps that one should take.

When the blood glucose level stays high consistently, it will gradually lead to the organ damage in long term.[30]

In terms of blood biochemical values, blood pressure and BMI, the results of this study showed that HbA1c, TG, CHOL-T and LDL-c were highly associated with the risk of DR in elderly patients with T2DM. On the other hand, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, HDL-c, eGFR and BMI were not significantly associated with the risk of DR. A study explained that the higher HbA1c increased the risk of DR, and hyperglycemia caused injury to body organs such as nerve damage (neuropathy) kidney damage (diabetic nephropathy), and even damage to the blood vessels of the retina (diabetic retinopathy), potentially leading to vision loses.[31] Stratton et al., (2000) pointed out that every 1% reduction of HbA1c could decrease the incidence of cerebrovascular accidents by 12%, the incidence of heart failure by 16%, the amputation or death caused by peripheral arterial occlusive disease by 43% and reduce the small blood vessel diseases by 37%.[32] One study in China also found that the higher systolic blood pressure, higher HbA1c, higher fasting plasma glucose, higher LDL-c and lower TG were important factors to increase the risk of DR. [33] However, another study in China also showed that higher systolic blood pressure, higher HbA1c, and lower body mass index were associated with the presence of DR.[34] A study from South Korean also confirmed that higher HbA1c was the significant risk factor for the incidence of DR risk in patients with T2DM.[28] Comparing to those results, the increased risk of DR was caused by higher HbA1c and higher LDL-c which were consistent with our study, but TG and CHOL-T were not. Thus, well control and manage for HbA1c and LDL-c should significantly decrease the chance of developing DR in diabetes or prevent from the progression of diabetic retinopathy in diabetes patients.[1,14,18,35,36]

Moreover, this study found that behavior of chewing betel nut was significantly associated with the development of DR in elderly patients with T2DM and was an essential predictor of DR. Some studies found that behavior of chewing betel nut was associated with the occurrence of chronic kidney disease, and increased the risk of cardiovascular disease.[37,38] Others found that chewing betel nut more frequently would increase the higher blood pressure and the behavior of chewing betel nut was also associated with an increased risk of arterial stiffness. [39,40] Therefore, it is probable to suggest that behavior of chewing betel nut could effect on small vessel disease and then it would cause the increasing of DR risk; and its relation with biological mechanism is worthy of further discussion.

This study found that the demographic characteristics in high risk group of developing DR were female, family history of diabetes, behavior of chewing betel nut and longer duration of diabetes; therefore, it would be suggested that patients with these factors should always keep their HbA1c, LDL-c, TG and CHOL-T in a normal range and give up their behaviors of chewing betel nut to prevent from developing DR. Besides, integrated care focusing on more coordinated and integrated forms of care provision would play an important role in the caring of patients with diabetes mellitus. Not only the blood glucose, blood pressure and blood lipid have to be regularly controlled and managed for patient with diabetes, but related complications of diabetes should also be regularly screened. However, anyone who had diabetes

mellitus was always under the risk of developing DR; and some cases of them will be diagnosed with DR after having diabetes mellitus for many years. Thus, it is important to enable the clinical care personnel to promote the regularly health examination for T2DM patients by exploring and understanding the important predictors of DR in patients with T2DM. The early intervention for vision problems is useful to prevent severe vision loss. Doctors should also allocate patients to appropriate hospitals or clinics in time, and for patients to attend to routine pupil examinations and consultations. Nurses should also implement the education of health guidelines individually upon patient's health condition. It will be helpful to improve and enhance the self-management abilities for patients' health as they were under the higher risk of the progression of DR.

Conclusions

In the past, many other studies focused on the betel nut chewing have been associated with oral cancer. Our study presents that behavior of chewing betel nut was one of the potential risk factors for DR in elderly patients with T2DM, which is very different from the other studies. Therefore, it is highly recommended to work on more investigation to explore the relationship between behavior of betel nut chewing and the risk of DR in diabetic patients in further.

List Of Abbreviations

Diabetic retinopathy (DR)

International Diabetes Federation (IDF)

Type 2 diabetes mellitus (T2DM)

Dilated fundus examination (DFE)

Glycated hemoglobin (HbA1c)

Triglyceride (TG)

Total cholesterol (CHOL-T)

High density lipoprotein cholesterol (HDL-c),

Low density lipoprotein cholesterol (LDL-c)

Estimated glomerular filtration rate (eGFR)

Body mass index (BMI)

Declarations

Ethics approval and consent to participate

This clinical study was approved by the local Ethics Committee and performed in accordance with the tenets of the Declaration of Helsinki. All patients gave their written informed consent form prior to inclusion to the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

There were no competing interests in this study.

Funding

There was no funding for this study.

Authors' contributions

All Authors had read and approved the manuscript, and their contributions were as the following:

YC undertaken the collection of data and drafted the manuscript.

TT shared the responsibility for the critical revision of the manuscript and provided statistical advice for the data from the inception of the study.

MS shared the responsibility for completing the final version of the manuscript and produced the statistical tables.

TY analyzed data and interpreted the results.

PT shared the responsibility for completing the final version of the manuscript and undertaken the collection of data.

CL provided the original idea, conception and design of study and making approval of final version of manuscript.

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Tables

Due to technical limitations, Tables 1 - 3 are only available for download from the Supplementary Files section.

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