A comparison of the risk factors of diabetic retinopathy between type 2 diabetes mellitus patients with and without metabolic syndrome

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Submitted: 19 December 2020
Accepted: 25 February 2021

Arch Med Sci
DOI: https://doi.org/10.5114/aoms/133705

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Abstract

Introduction: This study was aimed at analyzing, modeling, and comparing the risk factors of diabetic retinopathy (DR) among type 2 diabetes mellitus (DM) patients with and without metabolic syndrome (MS).
Material and methods: A cross-sectional study from July 2017 to July 2019 was performed by tracing type 2 DM patients who received treatment at an out-patient clinic and a mydriatic examination by an ophthalmologist in a single institute in south Taiwan. A total of 802 patients without DR were recruited and divided into two groups based on whether they had MS for this study. We analyzed the impact of DR based on the potential and related factors of these two groups.
Results: The sample consisted of 802 patients; 282 patients did not have MS, and 520 did. A comparison of the risk factors of DR among the patients with and without MS revealed that the level of glycated hemoglobin (HbA_{1c}) was a co-risk factor of DR. However, female sex, betel quid chewing, family history of DM, and higher total cholesterol were found to be risk factors of DR among the patients who had MS. Betel quid chewing, especially, could exacerbate the disease condition of DM and elevate the risk of DR.
Conclusions: Of those risk factors, betel quid chewing may be the main reason for DM deterioration and raised risk of DR. Hence, we recommend that the chewing of betel quid should be avoided to prevent DR.

Key words: type 2 diabetes mellitus, diabetic retinopathy, metabolic syndrome, betel quid chewing.

Introduction

Although betel quid chewing is culturally acceptable behavior, there are various serious complications that may follow, making it a health dilemma. Betel quid chewing increases the plasma concentrations of epinephrine and norepinephrine [1] due to which betel quid is one of the most widely abused psychoactive substances, used by an estimated 10–20% of the worldwide population [2]. Betel quid is the fourth most popular substance [3]. According to the WHO's estimates, 930 thousand people of the total population of 23 million in Taiwan use be-

tel quid [4]. There are a large number of studies that prove that betel quid chewing leads to negative health consequences, which may be attributed to its addictive and carcinogenic contents [5]. A meta-analysis that integrated 17 studies in Asia showed that betel quid chewing is associated with diabetes mellitus (DM), metabolic syndrome (MS), obesity, hypertension, cardiovascular diseases, and overall mortality [6]. A systemic review of eight studies revealed that betel quid chewing is associated with hyperglycemia and type 2 DM (in two studies), MS (in five studies), and obesity and weight gain (in four studies) [7]. With respect to MS, a study that was performed with 1,070 Pakistanis as the subjects revealed that betel quid chewing harms health and causes MS, especially when combined with the use of tobacco additives [8].

People with MS, which is also called insulin resistance syndrome, are five times more likely to suffer from type 2 DM and twice as likely to suffer from cardiovascular diseases as compared to healthy people [9–11]. Studies have shown that type 2 DM patients with comorbid MS have a higher risk of coronary artery disease than those who do not [12–15], as MS is primarily caused by obesity and insulin resistance. Insulin is responsible for glucose storage and usage, so insulin resistance leads to abnormalities in the metabolism of glucose [16]. Moreover, insulin resistance is also related to low-grade inflammation of the entire body, which causes a great impact on type 2 DM progression and micro- and macrovascular diseases [17–20]. Meanwhile, diabetic retinal venous thrombosis and retinal arteriolar stenosis are both associated with ocular stroke and coronary artery disease [21]. Thrombosis of retinal arterioles and capillaries is the leading cause of diabetic retinopathy (DR) and blindness in diabetic patients, particularly type 2 DM patients [22].

Many studies have proved that chewing betel quid increases the risk of type 2 DM, MS, and cardiovascular events. Moreover, the leading cause of DR is the poor control of DM. DR causes great impacts on the daily lives of type 2 DM patients. However, there is little evidence to support the correlation between betel quid chewing and DR.

The current study was focused on researching the correlation between betel quid chewing and DR with the aim of decreasing the incidence rate.

Material and methods

We included diabetic patients from type 2 DM and ophthalmology outpatient clinics in a single institute in south Taiwan between July 2017 and July 2019 in our cross-sectional study. The data were collected and analyzed based on the patients' demographic details, health-related behaviors, biochemical results, and bio-indexes related to MS. The biochemical results included DR and the average laboratory results 1 month before collection. At least once every 3 months, a set of survey questions was provided to the participating patients who visited the outpatient clinics for treatment. Their blood samples were also analyzed to determine the levels of glycated hemoglobin (HbA_{1c}), fasting glucose, triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) as well as the estimated glomerular filtration rate (eGFR). The surveys were targeted toward gathering standardized information about each patient's sex, body mass index (BMI), family history of DM, personal health history, and personal health habits.

BMI is a measure of body fat based on a person's height and weight (kg/m^2), and it was applied to most of the adults. Patients were considered to have a family history of DM if one (or both) of their parents had DM. The personal health history of each patient included their history of hypertension, cardiovascular disease, hyperlipidemia, and diabetic nephropathy for the purpose of this study. The health-related habits and lifestyle characteristics of the participants were also reviewed in the study, including their smoking, drinking, and betel chewing behaviors. Smoking behavior referred to cigarette use at least one time per day for over 6 months. Drinking behavior referred to a frequency of alcohol consumption up to three drinks per week for a period of over 6 months. Betel chewing behavior was attributed to participants who chewed on betel at least once per day for over 6 months. The subjects were considered to regularly exercise if they engaged in three exercise sessions of 30 min per week for over 6 months. The blood pressure assessment, which included systolic blood pressure (SBP) and diastolic blood pressure (DBP), was administered to the participants through a digital automatic blood pressure monitor. The creatinine, fasting glucose, triglyceride, total cholesterol, and HDL-c levels were examined on the analyzer (model 7180; Hitachi, Tokyo, Japan) using high-performance liquid chromatography. The eGFR parameter was based on the patient's serum creatinine level and a reliable indicator of renal function. The formula [$186 \times \text{creatinine}^{(-1.154)} \times \text{age}^{(-0.203)}$ ($\times$ 0.742 if female)] was used to calculate eGFR. In addition, LDL-c was often indirectly measured using a triglyceride, total cholesterol, and HDL-c formula.

Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and ap-

proved by the Institutional Review Board of Antai Medical Care Cooperation Antai-Tian-Sheng memorial Hospital (protocol code: 18-022-B, and date of approval: 31 March 2018).

Statistical analysis

We divided the diabetic patients into two groups based on whether they had MS, and their DR models were analyzed and constructed. Patients were determined to have MS if they had any three of the following criteria: (i) fasting glucose level was 100 mg/dl or greater; (ii) triglyceride level was 150 mg/dl or greater, (iii) SBP was 130 or greater and DBP was 85 mm Hg or greater; (iv) HDL-c was over 40 mg/dl in men and 50 mg/dl in women; or (v) waist circumference was over 90 cm in men and 80 cm in women [23]. The patients' characteristics were described in terms of mean and standard deviation values for continuous variables and absolute and relative frequencies for categorical variables. The normality tests of continuous variables, which included age, BMI, SBP, DBP, HbA_{1c}, fasting glucose, triglyceride, total cholesterol, HDL-c, LDL-c and eGFR, were analyzed by the Kolmogorov–Smirnov test, and all variables were underlying the data set to be normally distributed. For the inferential statistical analysis, we used the χ^2 test to test the association between DR and type 2 DM patients with and without MS. Logistic regression methods were applied to test the associations between the onset of DR and each related factor in a univariate analysis as well as to construct the DR models.

As a result, the important factors in each statistical test were taken into account for the DR models, and the optimal multivariable model was determined using the model selection method. The main results were summarized as a risk ratio with a confidence interval of 95%. The statistical results were considered to be significant when the *p*-value was less than 0.05. Moreover, *p*-values were 2-sided for overall statistical analysis in Results. IBM SPSS Statistics 24 was used to carry out the statistical analysis.

Results

There were 1,367 diabetic patients who visited the DM out-patient clinics and received at least once mydriatic retinal examination by the ophthalmologist every three months. Between July 2017 and July 2019, 565 patients were excluded from the study due to a history of DR (diagnosed before the current study), presence of non-diabetic glaucoma, history of gestational DM, pregnancy during the study, or presence of serious co-morbidities (heart failure, liver cirrhosis, severe infection, malignancy, etc.) (Figure 1). In the current study, the mean age was 67.86 ±11.10 years; 349 patients were male, 453 were female, 79 patients had betel quid chewing behavior, and 520 patients were affected by MS. Of the 621 patients with DR, there were 209 patients without MS and 412 patients with the syndrome (Table I). However, the DR rates among the type 2 DM patients with and without MS were 79.23% and 74.11%, respectively (χ^2 = 2.74, p = 0.098). Even if MS was not significantly associated with DR, it was worth separately comparing with the risk factors of DR among type 2DM patients with and without MS. Hypothetically, there should be different causes for occurrence of DR among type 2 DM patients with and without metabolic syndrome.

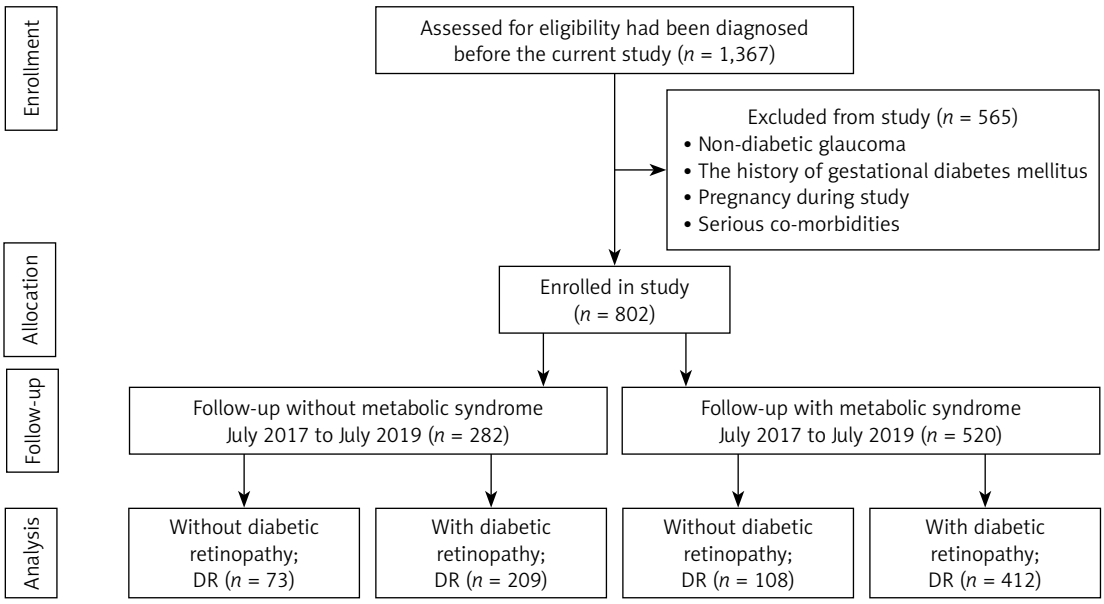

Figure 1. Flow diagram for the cross-sectional study of type 2 DM patients in Taiwan

Table I. Comparison of the categorical factors of DR between type 2 DM patients with and without metabolic syndrome

Items		Without metabolic syndrome					With metabolic syndrome				
		Without DR (*N* = 73)	**With DR (*N* = 209)**	**OR**	**95% CI**		**Without DR (*N* = 108)**	**With DR (*N* = 412)**	**OR**	**95% CI**	
		***n* (%)**	***n* (%)**		**Lower**	**Upper**	***n* (%)**	***n* (%)**		**Lower**	**Upper**
Sex	Male	50 (28.09)	128 (71.91)	1.38	0.78	2.43	45 (26.32)	126 (73.68)	1.62*	1.05	2.51
	Female	23 (22.12)	81 (77.88)				63 (18.05)	286 (81.95)			
Smoking	No	47 (23.86)	150 (76.14)	0.71	0.40	1.25	87 (21.07)	326 (78.93)	1.09	0.64	1.86
	Yes	26 (30.59)	59 (69.41)				21 (19.63)	86 (80.37)			
Alcohol	No	55 (24.89)	166 (75.11)	0.79	0.42	1.49	90 (20.83)	342 (79.17)	1.02	0.58	1.81
	Yes	18 (29.51)	43 (70.49)				18 (20.45)	70 (79.55)			
Betel quid	No	67 (26.38)	187 (73.62)	1.31	0.51	3.38	103 (20.96)	366 (78.04)	2.59*	1.00	6.66
	Yes	6 (21.43)	22 (78.57)				5 (9.80)	46 (90.20)			
Regular exercise	No	25 (21.74)	90 (78.26)	0.69	0.40	1.20	48 (20.96)	181 (79.04)	1.02	0.66	1.56
	Yes	48 (28.74)	119 (71.26)				60 (20.62)	231 (79.38)			
Family history of DM	No	34 (32.38)	71 (67.62)	1.69	0.99	2.91	54 (28.27)	137 (71.73)	2.01**	1.31	3.08
	Yes	39 (22.03)	138 (77.97)				54 (16.41)	275 (83.59)			
Hypertension	No	53 (24.88)	160 (75.12)	0.81	0.44	1.49	61 (20.89)	231 (79.11)	1.02	0.66	1.56
	Yes	20 (28.99)	49 (71.01)				47 (20.61)	181 (79.39)			
Cardiovascular disease	No	68 (25.09)	203 (74.91)	0.40	0.12	1.36	102 (20.94)	385 (79.06)	1.19	0.48	2.97
	Yes	5 (45.45)	6 (54.55)				6 (18.18)	27 (81.82)			
Hyperlipidemia	No	58 (26.24)	163 (73.76)	1.09	0.57	2.10	82 (20.97)	309 (79.03)	1.05	0.64	1.72
	Yes	15 (24.59)	46 (75.41)				26 (20.16)	103 (79.84)			
Diabetic nephropathy	No	72 (25.99)	205 (74.01)	1.41	0.15	12.78	107 (20.82)	407 (79.18)	1.31	0.15	11.37
	Yes	1 (20.00)	4 (80.00)				1 (16.67)	5 (83.33)			

*Values are β-coefficients (95% CIs) and p-values; DM – diabetes mellitus, DR – diabetic retinopathy; *p-value < 0.05, **p-value < 0.01.*

Among the type 2 DM patients without MS, there was no significant correlation between DR and the various variables (sex, smoking behavior, drinking behavior, betel quid chewing behavior, exercise, family history of DM, hypertension, heart disease, diabetic renal disease). However, among the patients with MS, the results revealed that each patient's sex, betel quid chewing behavior, and family history of DM were significantly correlated with the risk of DR. Female patients had a higher risk of suffering from DR than male patients (OR = 1.62, 95% CI: 1.05–2.51, $p = 0.029$); patients who chewed betel quid had a higher risk of suffering from DR than those who did not (OR = 2.59, 95% CI: 1.00–6.66, $p = 0.042$); patients with a family history of DM had a higher risk of suffering from DR than those without (OR = 2.01, 95% CI: 1.31–3.08, $p = 0.001$) (Table I).

The analysis of the risk factors of DR among the type 2 DM patients without MS showed higher HbA_{1c} levels (HbA_{1c} in DR/no-DR = 8.28%/7.60%, SD = 1.73/1.56) than in those without DR. Further, the univariate logistic regression analysis indicated that HbA_{1c} level (OR = 1.32, 95% CI: 1.09–1.60, $p = 0.004$) was associated with the presence of DR (Table II).

Among the type 2 DM patients with MS, level of HbA_{1c} and level of cholesterol were significantly correlated with the presence of DR. The patients with DR had higher HbA_{1c} levels (HbA_{1c} in DR/no-DR = 8.23%/7.70%, SD = 1.66/1.42) and higher cholesterol levels (cholesterol in DR/no-DR = 188.56/177.57 mg/dl, SD = 37.41/28.90) than those without DR. Further, the univariate logistic regression analysis indicated that the factors of HbA_{1c} level (OR = 1.27, 95% CI: 1.09–1.48, $p = 0.002$) and total cholesterol level (OR = 1.01, 95% CI: 1.00–1.02, $p = 0.005$) were associated with the presence of DR (Table II).

We set up the DR risk models according to the situation of MS among the type 2 DM patients and compared the risk factors that cause DR. In the model of the 520 type 2 DM patients with MS, the patient's sex, betel quid chewing behavior, family history of DM, HbA_{1c} level, and total cholesterol level were the major risk factors of DR. Among them, the patients who were female (OR = 2.64, 95% CI: 1.62–4.30, $p < 0.001$) or had betel quid chewing behavior (OR = 4.14, 95% CI: 1.51–11.34, $p = 0.006$), family history of DM (OR = 2.01, 95% CI: 1.33–3.06, $p = 0.001$), higher HbA_{1c} (OR = 1.25, 95% CI: 1.07–1.47, $p = 0.006$), or higher total cholesterol (OR = 1.01, 95% CI: 1.00–1.02, $p = 0.002$) were at an increased risk of DR (Table III).

In the model of the 282 type 2 DM patients without MS, only the level of HbA_{1c} was the major risk factor of DR. Further, higher HbA_{1c} levels (OR = 1.29, 95% CI: 1.06–1.56, $p = 0.012$) were found to increase the risk of DR among type 2 DM patients without MS. A comparison of these two models revealed that the level of HbA_{1c} was a co-risk factor for DR among type 2 DM patients. However, the patient's sex, betel quid chewing behavior, family history of DM, and cholesterol level were also risk factors for DR among the type 2 DM patients with MS. Betel quid chewing, especially, could exacerbate the disease condition of DM and elevate the risk of DR (Table III).

Finally, in the model of all the 802 patients, the patient's sex, betel quid chewing behavior, family history of DM, HbA_{1c} level, and total cholesterol level were the major risk factors of DR, which was similar to the model of the 520 type 2 DM patients with MS. Among them, the patients who were female (OR = 1.97, 95% CI: 1.35–2.86, $p < 0.001$) or had betel quid chewing behavior (OR = 2.44, 95% CI: 1.22–4.90, $p = 0.012$), family history of DM (OR = 1.78, 95% CI: 1.29–2.47, $p = 0.001$), higher HbA_{1c} levels (OR = 1.26, 95% CI: 1.11–1.42, $p < 0.001$), or higher total cholesterol levels (OR = 1.01, 95% CI: 1.00–1.01, $p = 0.004$) faced an increased risk of DR. However, there was no significant association between MS and the risk of DR among the type 2 DM patients (OR = 1.00, 95% CI: 0.69–1.46, $p = 0.993$) (Table III).

Discussion

According to an analysis of the risk factors and development of DR among type 2 DM patients in Korea in 2016, 44.9% of the patients developed DR, and 13.6% of the patients' conditions progressed to non-proliferative DR or proliferative DR. This study showed that the primary risk factors for the development of DR were old age, longer duration of DM, high HbA_{1c}, and high albuminuria. Sex, hypertension, diabetic nephropathy, cardiovascular disease, smoking, alcohol drinking, BMI, triglyceride, total cholesterol, HDL-c, LDL-c, and eGFR had no significant correlation with the incidence of DR [24]. In the current study, higher HbA_{1c} level was found to be the major risk factor for developing DR. This risk factor, which has been identified in several other studies, increases the risk of DR [25–29]. Moreover, our study also revealed that the patient's sex, betel quid chewing behavior, family history of DM, and total cholesterol level were significant risk factors for DR among type 2 DM patients with MS. However, we did not find any significant correlation between DR and hypertension, diabetic nephropathy, cardiovascular disease, smoking, alcohol drinking, BMI, triglyceride, HDL-c, LDL-c, or eGFR. Some researchers have pointed out that female type 2 DM patients face a higher risk of developing DR than male patients, and the same outcome was obtained in our study [25, 30]. However, a previously conducted study found no correlation between sex and DR [31].

Table II. Comparison of the continuous factors of DR between type 2 DM patients with and without metabolic syndrome

Items	Without metabolic syndrome						With metabolic syndrome					
	Without DR (*N* = 73)	With DR (*N* = 209)	*P*-value	OR	95% CI		Without DR (*N* = 108)	With DR (*N* = 412)	*P*-value	OR	95% CI	
	Mean (SD)	Mean (SD)			Lower	Upper	Mean (SD)	Mean (SD)			Lower	Upper
Age	68.47 (11.78)	66.27 (11.03)	0.152	0.98	0.96	1.01	70.19 (12.21)	67.95 (10.63)	0.059	0.98	0.96	1.00
BMI [kg/m^2]	24.39 (3.38)	24.17 (3.22)	0.617	0.98	0.90	1.06	27.25 (4.10)	27.24 (4.17)	0.991	1.00	0.95	1.05
SBP [mm Hg]	128.37 (18.59)	129.78 (19.77)	0.593	1.00	0.99	1.02	141.95 (17.50)	143.27 (19.74)	0.527	1.00	0.99	1.02
DBP [mm Hg]	72.68 (10.94)	73.03 (11.70)	0.826	1.00	0.98	1.03	78.69 (11.58)	79.84 (12.45)	0.384	1.01	0.99	1.03
HbA_{1c} (%)	7.60 (1.56)	8.28 (1.73)	0.004	1.32**	1.09	1.60	7.70 (1.42)	8.23 (1.66)	0.002	1.27**	1.09	1.48
Fasting glucose [mg/dl]	147.62 (47.48)	161.37 (101.95)	0.268	1.00	0.99	1.00	151.02 (56.52)	158.83 (61.17)	0.231	1.00	1.00	1.01
Triglyceride [mg/dl]	94.74 (32.14)	100.03 (48.67)	0.388	1.00	1.00	1.01	149.16 (58.99)	157.25 (80.75)	0.331	1.00	1.00	1.00
Total cholesterol [mg/dl]	172.90 (29.61)	182.20 (40.34)	0.072	1.01	1.00	1.02	177.57 (28.90)	188.56 (37.41)	0.005	1.01**	1.00	1.02
HDL-c [mg/dl]	55.86 (15.53)	56.41 (13.81)	0.779	1.00	0.98	1.02	47.52 (12.73)	48.72 (12.05)	0.365	1.01	0.99	1.03
LDL-c [mg/dl]	89.06 (24.47)	96.27 (32.44)	0.084	1.01	1.00	1.02	93.41 (23.13)	98.83 (28.58)	0.069	1.01	1.00	1.02
eGFR [ml/min/1.73 m^2]	76.35 (21.54)	75.05 (25.91)	0.705	1.00	0.99	1.01	69.31 (20.59)	68.11 (27.73)	0.682	1.00	0.99	1.01

*Values are β-coefficients (95% CIs) and p-values; type 2 DM – type 2 diabetes mellitus, DR – diabetic retinopathy, BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, HbA_{1c} – glycated hemoglobin, HDL-c – high-density lipoprotein cholesterol, LDL-c – low-density lipoprotein cholesterol, eGFR – estimated glomerular filtration rate, **p-value < 0.01; ***p-value < 0.001.*

Table III. Logistic regression models of the risk factors for DR between type 2 DM patients with and without metabolic syndrome

Models	Without metabolic syndrome (*N* = 282)			With metabolic syndrome (*N* = 520)			All data (*N* = 802)		
Variables (reference)	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
MS (No)							1.00	0.69, 1.46	0.993
Sex (male)	1.39	0.76, 2.54	0.286	2.64***	1.62, 4.30	<.001	1.97***	1.35, 2.86	< 0.001
Family history of DM (No)	1.55	0.91, 2.62	0.106	2.01**	1.33, 3.06	0.001	1.78**	1.29, 2.47	0.001
Betel quid (No)	1.35	0.50, 3.65	0.558	4.14**	1.51, 11.34	0.006	2.44*	1.22, 4.90	0.012
Total cholesterol	1.01	0.99., 1.02	0.270	1.01**	1.00, 1.02	0.002	1.01**	1.00, 1.01	0.004
HbA_{1c}	1.29*	1.06, 1.56	0.012	1.25**	1.07, 1.47	0.006	1.26***	1.11, 1.42	< 0.001

*Values are β-coefficients (95% CIs) and p-values; type 2 DM – type 2 diabetes mellitus, DR – diabetic retinopathy, HbA_{1c} – glycated hemoglobin; *p-value < 0.05; **p-value < 0.01; ***p-value < 0.001.*

In a study on the risk factors and prevalence of DR in Beijing, China, 18.8% of the type 2 DM patients were found to suffer from DR. The incidence of DR was found to be higher among younger patients with longer DM durations, higher fasting blood sugar levels, higher post-prandial two-hour blood sugar levels, higher SBP, higher total cholesterol, higher LDL-c, higher BUN, lower BMI, and more microalbuminuria [32]. Another study in China revealed that younger age, longer DM duration, higher fasting blood sugar and HbA_{1c} levels, higher SBP, and lower HDL-c and triglyceride levels were related to higher incidence of DR [33]. Integrating these two studies and our study, the factors of DM duration, blood pressure, lipid profile, and blood sugar level are related to a high risk of DR. This indicates that diabetic patients should pay more attention to their blood pressure and sugar and lipid profiles to better control the disease and lower the risk of diabetic complications [28, 32–34].

The results obtained from our current study emphasized that betel quid chewing and family history of DM are risk factors for developing DR, because there have been only a few related studies discussing these two factors in relation to DR. However, the correlation between the incidence of DM and family history of DM has previously been confirmed, which means that people with a family history of DM are at a higher risk of DM [30, 35]. Moreover, an animal study revealed that betel quid chewing may lead to impaired fasting glucose. This phenomenon is caused by the nitrosamine in betel quid, which induces the development of DM [36]. The recline can inhibit adipogenesis and interfere with insulin-related glucose uptake, which means that the recline may lead to hyperlipidemia, hyperglycemia, or insulin resistance by inducing adipocyte dysfunction [37]. There is evidence to show that insulin resistance is related to low-grade systemic inflammation [38–40]. Low-grade systemic inflammation plays an important role in the pathogenesis of incidence, disease progression, and microvascular and macrovascular dysfunction in type 2 DM patients with MS [18, 19, 41]. A series of mechanisms explain that betel quid chewing may be a major cause of disease progression, leading to DR among type 2 DM patients with MS, which corresponds to the results obtained from the current study.

We highly suspect that unhealthy social cultures (such as betel quid chewing) are associated with DM deterioration. According to the literature review, the mechanism through which betel quid causes molecular damage in the human body and worsens the disease condition of MS and DM has become clear. Our study also showed the same association between betel quid chewing and the progression of DM, proving that betel quid chewing increases the incidence of DR. We hypothesize that the compounds in betel quid attenuate the effects of drugs that treat hypertension, DM, and hyperlipidemia. The current study could be used as a reference by policymakers and public health units for the prevention and control of betel use, interventions against quit betel quid chewing, and the promotion of healthy lifestyles. Further research for the exploration of the interactions between betel quid and various medications is recommended.

Our research had some limitations. The patient's recruitment might not represent the overall diabetes patients, since this study was conducted in a tertiary care hospital. We were concerned about missing data, including lifestyle modifications and adherence, having employed a cross-sectional study design. The residual confounding factors cannot be excluded due to unmeasured factors. However, compared to other studies it was very specially to find that betel quid chewing behavior was one of the potential risk factors for DR in type 2 DM patients, especially in MS patients. It is necessary to have a more extensive population study for better understanding of the relationship between DR and relative risk factors.

In conclusion, this study showed that the patient's sex, betel quid chewing behavior, family history of DM, HbA_{1c} level, and total cholesterol level were vital factors for the development of DR in type 2 DM patients, especially in MS patients; and most of the findings were consistent with risk factors reported in existing literature. Furthermore, we also found the behavior of chewing betel nut to be a unique risk factor to the Taiwanese population. We suggested that patients should control their HbA_{1c} and total cholesterol and quit betel quid chewing behavior to prevent DR.

Conflict of interest

The authors declare no conflict of interest.

References

1. Chu NS. Effect of betel chewing on the central and autonomic nervous systems. J Biomed Sci 2001; 8: 229-36.
2. Lin CF, Wang JD, Chen PH, et al. Predictors of betel quid chewing behavior and cessation patterns in Taiwan aborigines. BMC Public Health 2006; 6: 271.
3. Chen SH, Lee JM, Liu HH, Wang HC, Ye CY. The cross-effects of cigarette and betel nut consumption in Taiwan: have tax increases made a difference? Health Policy Plan 2011; 26: 266-73.
4. Health Promotion Administration, Ministry of Health and Welfare (2015) Health promotion administration annual report. http://health99.hpa.gov.tw/media/public/pdf/21791.pdf. [Accessed :19.01.2017].
5. Tham J, Sem G, Sit E, Tai MC. The ethics of betel nut consumption in Taiwan. J Med Ethics 2017; 43: 739-40.
6. Yamada T, Hara K, Kadowaki T. Chewing betel quid and the risk of metabolic disease, cardiovascular dis-

ease, and all-cause mortality: ameta-analysis. PLoS One 2013; 8: e70679.
7. Javed F, Al-Hezaimi K, Warnakulasuriya S. Areca-nut chewing habit is a significant risk factor for metabolic syndrome: a systematic review. J Nutr Health Aging 2012; 16: 445-8.
8. Shafique K, Zafar M, Ahmed Z, Naveed AK, Muhammad AM, Fauzia I. Areca nut chewing and metabolic syndrome: evidence of a harmful relationship. Nutr J 2013; 12: 67.
9. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med 2006; 119: 812-9.
10. Samson SL, Garber AJ. Metabolic syndrome. Endocrinal Metab Clin North Am 2014; 43: 1-23.
11. Katsiki N, Anagnostis P, Kotsa K, Goulis DG, Mikhailidis DP. Obesity, metabolic syndrome and the risk of microvascular complications in patients with diabetes mellitus. Curr Pharm Des 2019; 25: 2051-9.
12. Alexander CM, Landsman PB, Teutsch SM, Steven MH. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III particiipants age 50 years and older. Diabetes 2003; 52: 1210-4.
13. Katakami N, Kaneto H, Funahashi T, Iichiro S. Type 2 diabetes and atherosclerosis: focusing on metabolic syndrome. Diabetol Int 2013; 4: 143-8.
14. Sergi, Chiu B, Feulefack J, Shen F, Chiu B. Usefulness of resveratrol supplementation in decreasing cardiometabolic risk factors comparing subjects with metabolic syndrome and healthy subjects with or without obesity: meta-analysis using multinational, randomised, controlled trials. Arch Med Sci Atheroscler Dis 2020; 5: e98-111.
15. Katsiki N, Banach M, Mikhailidis DP. Is type 2 diabetes mellitus a coronary heart disease equivalent or not? Do not just enjoy the debate and forget the patient! Arch Med Sci 2019; 15: 1357-64.
16. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006; 444: 881-7.
17. Haffner SM. The metabolic syndrome: inflammation, diabetes mellitus, and cardiovascular disease. Am J Cardiol 2006; 97: 3A-11A.
18. Kahn SE, Zinman B, Haffner SM, et al. Obesity is a major determinant of the association of C-reactive protein levels and the metabolic syndrome in type 2 diabetes. Diabetes 2006; 55: 2357-64.
19. Pourfarzam M, Zadhoush F, Sadeghi M. The difference in correlation between insulin resistance index and chronic inflammation in type 2 diabetes with and without metabolic syndrome. Adv Biomed Res 2016; 5: 153.
20. Wierzba W, Pinkas J, Karnafel W, dziemidok P, Jawień A, Śliwczynski A. Evaluation of the incidence of aortic aneurysms in patients with and without diabetes in Poland in 2012 based on the database of the National Health Fund. Arch Med Sci 2019; 15: 607-12.
21. Ogagarue ER, Lutsey PL, Klein R, Kunihiro M, Folsom AR. Association of ideal cardiovascular health metrics and retinal microvascular findings: the atherosclerosis risk in communities study. J Am Heart Assoc 2013; 19: e000430.
22. Sánchez-Thorin JC. The epidemiology of diabetes mellitus and diabetic retinopathy. Int Ophthalmol Clin 1998; 38: 11-8.
23. Kassi E, Pervanidou P, Kaltas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC 2011; 9: 48.
24. Yun JS, Lim TS, Cha SA, et al. Clinical course and risk factors of diabetic retinopathy in patients with type 2 diabetes mellitus in Korea. Diabetes Metab J 2016; 40: 482-93.
25. Sheu SJ, Liu NC, Ger LP, David M. High HbA1c level was the most important factor associated with prevalence of diabetic retinopathy in Taiwanese type II diabetic patients with a fixed duration. Graefes Arch Clin Exp Ophthalmol 2013; 251: 2087-92.
26. Wat N, Wong RL, Wong IY. Associations between diabetic retinopathy and systemic risk factors. Hong Kong Med J 2016; 22: 589-99.
27. Voigt M, Schmidt S, Lehmann T, et al. Prevalence and progression rate of diabetic retinopathy in type 2 diabetes patients in correlation with the duration of diabetes. Exp Clin Endocrinol Diabetes 2018; 126: 570-6.
28. Chew EY, Ambrosius WT, Davis MD, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med 2010; 363: 233-44.
29. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010; 376: 124-36.
30. López M, Cos FX, Álvarez-Guisasola F, Eva F. Prevalence of diabetic retinopathy and its relationship with glomerular filtration rate and other risk factors in patients with type 2 diabetes mellitus in Spain. DM2 HOPE study. J Clin Transl Endocrinol 2017; 9: 61-5.
31. Zhang G, Chen H, Chen W, Mingzhi Z. Prevalence and risk factors for diabetic retinopathy in China: a multi-hospital-based cross-sectional study. Br J Ophthalmol 2017; 101: 591-5.
32. Xu J, Wei WB, Yuan M X, et al. Prevalence and risk factors for diabetic retinopathy: the Beijing communities diabetes study 6. Retina 2012; 32: 322-9.
33. Chung YR, Park SW, Choi SY, et al. Association of statin use and hypertriglyceridemia with diabetic macular edema in patients with type 2 diabetes and diabetic retinopathy. Cardiovasc Diabetol 2017; 16: 4.
34. Srinivasan S, Raman R, Kulothungan V, Gayathri S, Sharma T. Influence of serum lipids on the incidence and progression of diabetic retinopathy and macular oedema: Sankara Nethralaya diabetic retinopathy epidemiology and molecular genetics study-II. Clin Exp Ophthalmol 2017; 45: 894-900.
35. Cheng H, Treglown L, Montgomery S, Adrian F. Associations between familial factor, trait conscientiousness, gender and the occurrence of type 2 diabetes in adulthood: evidence from a British cohort. PLoS One 2015; 10: e0122701.
36. Scott RA, Langenberg C, Sharp SJ, et al. The link between family history and risk of type 2 diabetes is not explained by anthropometric, lifestyle or genetic risk factors: the EPIC-InterAct study. Diabetologia 2013; 56: 60-9.
37. World Health Organization Diabetes. http://www.who.int/mediacentre/factsheets/fs312/en. Accessed: 23.12.2017.
38. Boucher BJ, Ewen SW, Stowers JM. Betel nut (Areca catechu) consumption and the induction of glucose intolerance in adult CD1 mice and in their F1 and F2 offspring. Diabetologia 1994; 37: 49-55.
39. Meshkani R, Adeli K. Hepatic insulin resistance, metabolic syndrome and cardiovascular disease. Clin Biochem 2009; 42: 1331-46.
40. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract 2014; 105: 141-50.
41. Steven MH. The metabolic syndrome: Inflammation, diabetes mellitus, and cardiovascular disease. Am J Cardiol 2006; 97: 3-11.