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Original Article

Synergistic effect of blood lipids and uric acid on periodontitis in patients with type 2 diabetes

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Abstract: Objective: This study investigated the interaction of dyslipidemia and hyperuricemia on periodontitis in patients with type 2 diabetes mellitus (T2DM). Methods: The clinical data of 220 patients with T2DM (diabetes group) treated in Tianjin Baodi Hospital from January 2019 to December 2021 were retrospectively analyzed. Another 200 healthy subjects in the same period were selected as the control group. The correlation of hyperuricemia and hyperlipidemia with diabetes was tested by the spearman correlation coefficient. Multivariate logistic regression was used to analyze the multiplicative interaction and additive interaction of dyslipidemia and hyperuricemia on periodontitis. Results: Diabetes was positively correlated with hyperuricemia and hyperlipidemia ($P<0.05$). Patients with dyslipidemia (OR = 8.107, 95% CI: 2.687-24.457) and hyperuricemia (OR = 2.940, 95% CI: 0.970-8.909) had a higher risk of periodontitis, but there was no multiplicative interaction effect of dyslipidemia and hyperuricemia on periodontitis (OR = 1.864, 95% CI: 0.256-13.545, $P>0.05$). The risk of developing diabetes was higher in individuals with dyslipidemia and hypertension than in those without (OR = 2.887, 95% CI: 1.478-4.855). The evaluation indexes of the combined interaction effect relative excess risk due to interaction, interaction attribution percentage and synergy index were 0.902 (95% CI: 0.379-1.496), 0.273 (95% CI: 0.106-0.458) and 1.485 (95% CI: 0.978-2.165), respectively. Conclusion: Dyslipidemia and hyperuricemia may have a synergistic effect on periodontitis in people with T2DM. Improving blood lipids and controlling blood uric acid may synergistically prevent periodontitis.

Keywords: Blood lipid level, blood uric acid level, T2DM, periodontitis, interaction

Introduction

Periodontal disease and diabetes are both very common chronic diseases, resulting in a large amount of human and material investment in public health services. With the change in human lifestyles, the morbidity of diabetes is also gradually increasing. According to WHO data, at least 2.8% of the world population suffer from diabetes [1]. The number of diabetic individuals in China now ranks first in the world. Chronic periodontitis is a multifactorial infectious disease with plaque as the initiating factor. Its occurrence and development have a two-way relationship with systemic diseases. Research on the interaction between type 2 diabetes mellitus (T2DM) and periodontitis has been ongoing for over 50 years. Patients with uncontrolled or poorly controlled blood sugar are more likely to suffer from severe periodontitis. Compared with non-diabetic individuals, diabetics are more likely to develop a systemic infection, and the morbidity of periodontal disease in diabetics is about 3 times higher [2]. Periodontitis directly affects the severity of complications of diabetes by negatively regulating blood sugar in diabetes patients. The abnormal lipid metabolism and blood coagulation caused by periodontitis may also affect the degree of microvascular disease in diabetes patients.

Periodontitis itself, due to the release of bacterial metabolites into the whole blood circulation, will lead to the increase of inflammatory factors, which will affect the metabolism of body lipid indicators and have a negative impact on body health [3]. Therefore, diabetics

with periodontal disease are more likely to have lipid metabolism disorders, and glucose metabolism disorders are more serious. At the same time, the disorder of blood glucose and blood lipid metabolism will aggravate the severity of the periodontal disease. There is insulin resistance in patients with T2DM, and their uric acid excretion is reduced because of hyperinsulinemia, resulting in increased blood uric acid levels [4]. High levels of serum uric acid can aggravate the systemic inflammatory state in people with periodontitis, which can further affect the periodontal local microenvironment [5]. Dyslipidemia and high blood uric acid levels are both independent risk factors for periodontitis in patients with T2DM.

The mechanism of interaction between periodontitis and diabetes is not completely clear, but both of them involve pathophysiological processes such as immune inflammatory reaction, microcirculatory disorders and thickening of capillary basement membrane. Due to the corresponding pathological changes of micro vessels in diabetes patients, they usually have abnormal blood lipids and blood uric acid, which increase the risk of aggravating microvascular diseases. The following questions are important in this research: What is the abnormality degree of blood lipids and uric acid in diabetes patients? Does it affect the occurrence of periodontitis? Is there a synergistic effect of blood lipids and uric acid on the risk of periodontitis? What is the specific impact mechanism? These issues have always been the focus of clinical research, but there are few reports on whether the two factors will increase the risk of periodontitis in patients with T2DM. The ability of data on the prevention of T2DM complicated with periodontitis is still weak, and more clinical data on the risk factors of periodontitis is needed to help identify high-risk patients efficiently in order to take timely intervention measures. Therefore, this research aimed to investigate the interaction between dyslipidemia and hyperuricemia on periodontitis in patients with T2DM and to offer a scientific basis for the prevention and control of periodontitis in sufferers with T2DM.

Materials and methods

Research subjects

The clinical data of 220 individuals with T2DM (diabetes group) treated in Tianjin Baodi Hospital from January 2019 to December 2021 were retrospectively analyzed. Inclusion criteria: (1) The patients met the clinical diagnostic criteria for T2DM; (2) patients who had no acute or chronic inflammation in other parts of the body except for periodontitis; (3) patients who provided complete case data. Exclusion criteria: (1) individuals with acute diabetic complications such as diabetic ketoacidosis; (2) individuals with other systemic diseases affecting periodontal health; (3) those with severe cardiac, liver or kidney insufficiency; (4) those with malignant tumors or acute cardiovascular and cerebrovascular diseases. In addition, 200 healthy subjects who underwent physical examination in Tianjin Baodi Hospital during the same period with similar baseline data to the T2DM patients were selected as control group. This study was approved by the Ethics Committee of Tianjin Baodi Hospital.

Methods

Data from all subjects were collected, including basic information, lifestyle (smoking, drinking), medication history and medical history. Body measurements included height, weight, waist circumference, blood pressure, and body mass index (BMI). Blood pressure was measured by an HBP-1300 electronic sphygmomanometer (Omron, Japan). Blood glucose was measured by Baijie PD-G001-2 fast blood glucose meter (Qinli Biotechnology Co., Ltd.). CardiocheckPA rapid blood lipid tester (Shanghai Maipuri Biotechnology Co., Ltd.) was used to conduct 4 rapid blood lipid tests, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). An automatic biochemical analyzer (Shenzhen Mindray bs-300) was used to detect the level of uric acid in the blood. The double reagent rate method was used and operated in strict accordance, and indoor quality control was performed at the same time.

Related definitions

Diagnostic criteria for periodontitis: one of the detection sites (the mesial, central and distal sites on the buccal and lingual sides) met the clinical attachment loss ≥2 mm, and those who did not meet the condition were considered as non-periodontal disease. Dyslipidemia: those with TC ≥Co2 mmol/L, TG ≥G 3 mmol/L, HDL-C <1.0 mmol/L, LDL-C ≥DL1 mmol/L, self-report-

Table 1. Proportion of hyperuricemia and hyperlipidemia patients in the diabetes group and the control group [n (%)]

Group	n	Hyperuricemia	Hyperlipidemia
Control group	200	68 (34.00)	75 (37.50)
Diabetic group	220	166 (75.45)	161 (73.18)
χ^2		64.864	54.183
P		<0.001	<0.001

Table 2. Correlation of diabetes mellitus with hyperuricemia and hyperlipidemia

Type	Diabetic	
	r	*P*
Hyperuricemia	0.602	0.005
Hyperlipidemia	0.668	<0.001

ed history of dyslipidemia, or administration of lipid-lowering drugs within the past 2 weeks. Hyperuricemia: male blood uric acid >420 μmol/L, female blood uric acid >360 μmol/L. Smoking: Respondents self-reported that they currently smoked and that the cumulative number of cigarettes smoked in the past exceeded 100 cigaretts. Central obesity: Waist circumference ≥85 cm for women and ≥90 cm for men. Overweight or obese: BMI ≥24 kg/m^2. Alcohol consumption: drinking frequency ≥2 times per week in the past 1 year.

Statistical methods

SPSS 22.0 was adopted for statistical analysis. Enumeration data were expressed as rates, and the χ^2 test was used for comparison between groups. The correlation of T2DM with hyperuricemia and hyperlipidemia was tested by the spearman correlation coefficient. Multivariate logistic regression was used to analyze the multiplicative and additive interactions of dyslipidemia and hyperuricemia on periodontitis. The expression of the logistic regression model with the interaction term in the multiplicative interaction was: logit $P = \alpha+\beta_d\times D+\beta_h\times H+\beta_{dh}\times D\times H$, where D and H represent dyslipidemia and hyperuricemia, respectively, and the Odds Ratio (OR) was used. The 95% confidence interval (CI) was used to evaluate the multiplicative interaction effect, $OR_{int} = \exp(\beta_{dh})$. If the 95% CI of OR_{int} did not contain 1, a multiplicative interaction effect was indicated. An additive model was used to convert the research factors dyslipidemia and hyperuricemia into dyslipidemia and no hyperuricemia (Dum_{10}), non-dyslipidemia and hyperuricemia (Dum_{01}), and dyslipidemia and hyperuricemia (Dum_{11}). The 3 dummy variable types were included in the model. The additive interaction effect was evaluated by relative excess risk due to interaction (RERI), interaction attribution percentage (AP), synergy index (SI) and 95% CI. Their calculation formulas are: $RERI = OR_{11}-OR_{01}-OR_{10}+1$, $AP = RERI/OR_{11}$, $SI = (OR_{11}-1)/([OR_{01}-1)+(OR_{10}-1)]$. When 95% CI of RERI and AP did not contain 0 and 95% CI of SI did not contain 1, an additive interaction effect was indicated. $P<0.05$ was considered a significant difference.

Results

Correlation of T2DM with hyperuricemia and hyperlipidemia

Among the 220 patients with T2DM, 161 (73.18%) had hyperlipidemia and 166 (75.45%) had hyperuricemia. In the control group, there were 75 patients with hyperlipidemia (37.50%) and 68 patients with hyperuricemia (34.00%). The proportions of patients with hyperuricemia and hyperlipidemia were statistically different between the two groups ($P<0.05$). as shown in **Table 1**. The Spearman correlation coefficient was used to test the correlation of diabetes with hyperuricemia and hyperlipidemia. The results showed that diabetes was positively correlated with hyperuricemia and hyperlipidemia ($P<0.05$), as shown in **Table 2**.

Comparison of basic characteristics of patients with T2DM

Among the 220 sufferers with T2DM, there were 163 sufferers (74.09%) with periodontitis, 161 sufferers (73.18%) with dyslipidemia, and 166 sufferers with hyperuricemia (75.45%). No significant difference was shown in sex, education level and smoking history between the non-periodontitis group and the periodontitis group ($P>0.05$). Which significant differences were found in age, overweight or obesity, alcohol consumption, cardiovascular disease history, hypertension, dyslipidemia and hyperuricemia between these two groups ($P<0.05$) (**Table 3**).

Table 3. Comparison of basic characteristics of the research subjects [n (%)]

Feature	Non-periodontitis group (n = 57)	Periodontitis group (n = 163)	χ^2	*P*
Sex				
Male	32 (26.45)	89 (73.55)		
Female	25 (25.25)	74 (74.75)	0.040	0.841
Age (years)				
<60	38 (31.40)	83 (68.60)		
≥60	19 (19.19)	80 (80.81)	4.231	0.040
Educational level				
Junior high school and below	40 (27.78)	104 (72.22)		
High school or secondary school	12 (21.82)	43 (78.18)		
College and above	5 (23.81)	16 (76.19)	0.790	0.674
Overweight or obese				
No	23 (37.10)	39 (68.42)		
Yes	34 (21.52)	124 (76.07)	5.629	0.018
Smokers				
No	30 (21.90)	107 (78.10)		
Yes	27 (32.53)	56 (67.47)	3.044	0.081
Drinking				
No	22 (42.31)	30 (57.69)		
Yes	35 (20.83)	133 (79.17)	9.539	0.002
Cardiovascular history				
No	19 (42.22)	26 (57.78)		
Yes	38 (21.71)	137 (78.29)	7.843	0.005
Hypertension				
No	22 (36.67)	38 (63.33)		
Yes	35 (21.88)	125 (78.13)	4.974	0.026
Dyslipidemia				
No	39 (66.10)	20 (33.90)		
Yes	18 (11.18)	143 (88.82)	67.846	<0.001
Hyperuricemia				
No	36 (66.67)	18 (33.33)		
Yes	21 (12.65)	145 (87.35)	61.931	<0.001

Table 4. Logistic regression model variable assignments

Variable	Assign
Sex	0 = male, 1 = female
Age (years)	0 = <60, 1 = ≥ 0
Educational level	1 = junior high school and below, 2 = high school or technical secondary school, 3 = junior college and above
Overweight or obese	0 = no, 1 = yes
Drinking	0 = no, 1 = yes
Cardiovascular history	0 = no, 1 = yes
Hypertension	0 = no, 1 = yes
Dyslipidemia	0 = no, 1 = yes
Hyperuricemia	0 = no, 1 = yes
Periodontitis	0 = no, 1 = yes

Association analysis of dyslipidemia and hyperuricemia with periodontitis

Taking the presence or absence of periodontitis as the dependent variable, and dyslipidemia and hyperuricemia as independent variables, the univariate logistic regression analysis demonstrated that dyslipidemia and hyperuricemia acid were both associated with a high risk of periodontitis ($P<0.001$).

Multivariate logistic regression analysis was conducted with age, being overweight or obesity, drinking, cardiovascular history, hypertension, dyslipidemia

Table 5. Logistic regression analysis of the association of dyslipidemia, hyperuricemia with periodontitis

Variable	Single factor		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Dyslipidemia				
No	1.00	_	1.00	_
Yes	15.492 (7.476, 32.101)	<0.001	8.107 (2.687, 24.457)	0.009
Hyperuricemia				
No	1.00	_	1.00	_
Yes	13.810 (6.670, 28.590)	<0.001	2.940 (0.970, 8.909)	0.024

Table 6. Multiplicative interaction of dyslipidemia and hyperuricemia on periodontitis

Variable	Model[a]		Model[b]	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Dyslipidemia	5.960 (1.007, 35.267)	0.029	4.231 (0.881, 20.309)	0.035
Hyperuricemia	2.439 (0.604, 9.854)	0.041	2.962 (0.836, 10.496)	0.044
Dyslipidemia × Hyperuricemia	1.604 (0.182, 14.138)	0.237	1.864 (0.256, 13.545)	0.314

Note: a means unadjusted for other variables; b means adjusted for age, overweight or obesity, alcohol consumption, cardiovascular history, and hypertension.

and hyperuricemia as independent variables. The results showed that patients with dyslipidemia (OR = 8.107, 95% CI: 2.687-24.457) and hyperuricemia (OR = 2.940, 95% CI: 0.970-8.909) had a higher risk of periodontitis, with statistical significance (*P*<0.01). The variable assignments are shown in **Table 4**, and the logistic regression analysis results are shown in **Table 5**.

Multiplicative interaction of dyslipidemia and hyperuricemia on periodontitis

Taking periodontitis as the dependent variable, dyslipidemia, hyperuricemia and dyslipidemia × hyperuricemia as independent variables to the logistic regression model, model 1 and model 2 were constructed. The results demonstrated that after adjusting for confounding factors, dyslipidemia and hyperuricemia had signifi-cant effects on the morbidity of periodontitis (*P*<0.05). However, there was no multiplicative interaction effect of dyslipidemia and hyperuricemia on periodontitis, without a significant difference (*P*>0.05) (**Table 6**).

The additive interaction of dyslipidemia and hyperuricemia on periodontitis

Dyslipidemia and hyperuricemia were replaced with 3 dummy variables which were then included in the regression model to obtain the OR value and its 95% CI, and the three indicators and 95% CI for evaluating the additive interaction were calculated according to the formula. After adjusting for relevant variables, the results demonstrated that the risk of periodontitis in sufferers with dyslipidemia and hyperuricemia was higher than that in sufferers without (OR = 2.887, 95% CI: 1.478-4.855). When dyslipidemia and hyperuricemia both existed, the risk of periodontitis was higher than the sum of the risks caused by the two alone (RERI = 0.902, 95% CI: 0.379-1.496), and the synergistic effect was 1.485 times the sum of the effects of the two alone (SI = 1.485,95% CI: 0.978-2.165). It was found that 27.3% of the risk of periodontitis in the presence of both was attributed to their synergistic effect (AP = 0.273, 95% CI: 0.106-0.458) (**Tables 7** and **8**).

Discussion

Diabetes and periodontal disease are both common diseases with high morbidity that seriously endanger human health. Periodontal disease is both a risk factor for diabetes and a complication of diabetes [6]. Diabetes reduces the body's healing ability and anti-infection ability by affecting the body's glucose metabolism, making the periodontal tissue susceptible to infection and destruction by bacteria and other pathogens, thus leading to an increased

Table 7. Additive interaction of dyslipidemia and hyperuricemia on periodontitis

Dyslipidemia	Hyperuricemia	Periodontitis (n)	Non-periodontitis (n)	Model[a]		Model[b]	
				OR (95% CI)	*P*	OR (95% CI)	*P*
No	No	138	16	1.00	_	1.00	_
Yes	No	7	5	1.818 (1.642, 3.831)	0.004	1.667 (1.002, 4.087)	0.002
No	Yes	5	3	2.144 (1.776, 4.117)	0.019	1.917 (1.164, 3.976)	0.015
Yes	Yes	13	33	2.583 (1.824, 4.267)	0.036	2.887 (1.478, 4.855)	0.021

Note: a means unadjusted for other variables; b means adjusted for age, overweight or obesity, alcohol consumption, cardiovascular history, and hypertension.

Table 8. Evaluation indicators of additive interaction

Model	RERI (95% CI)	AP (95% CI)	SI (95% CI)
Model[a]	1.212 (0.534, 2.017)	0.314 (0.159, 0.542)	1.639 (1.086, 2.341)
Model[b]	0.902 (0.379, 1.496)	0.273 (0.106, 0.458)	1.485 (0.978, 2.165)

Note: a means unadjusted for other variables; b means adjusted for age, overweight or obesity, alcohol consumption, cardiovascular history, and hypertension. RERI: Relative Excess Risk due to Interaction; AP: Attribution Percentage; SI: Synergy Index.

morbidity of periodontal disease in the diabetic population [7]. There are many previous studies on the influencing factors of periodontitis in diabetes, but there are few studies on the interaction of related risk factors on periodontitis. Dyslipidemia and hyperuricemia are independent risk factors for periodontitis. This research analyzed the effect of the interaction of dyslipidemia and hyperuricemia on periodontitis. The results demonstrated that both dyslipidemia and hyperuricemia were associated with periodontal disease. There was an additive interaction of dyslipidemia and hyperuricemia on periodontitis. That is, the risk of periodontitis in patients with both dyslipidemia and hyperuricemia was higher than the sum of the individual effects of dyslipidemia and hyperuricemia alone. This is similar to the results of a previous study [8].

This research demonstrated that after adjusting for relevant variables, the risk of periodontitis in patients with dyslipidemia was 8.107 times higher than that in those with normal blood lipids. It has been reported that blood lipid levels have a correlation with periodontitis, but the results are still inconclusive. Studies have shown [9] that the total cholesterol and TG levels in patients with periodontitis are higher than those in healthy individuals, indicating that infection may affect lipid metabolism, thereby increasing the level of blood lipids. Another study demonstrated that [10] the TG level of patients with aggressive periodontitis was higher than that of the healthy group, and the total cholesterol of patients with aggressive periodontitis was positively correlated with the percentage of severe sites, suggesting that infection may affect lipid metabolism and increase the levels of TG in plasma. Nassar et al. [11] have pointed out that hyperlipidemia is a common risk factor for chronic periodontitis and diabetes, and diabetics often have clinical manifestations of elevated TG and decreased TC, while periodontitis also increases the levels of TG and TC *in vivo*. Sgolastra et al. [12] found that the levels of TC, TG and LDL were higher, and the level of HDL was lower in the blood of diabetics with periodontitis than those without, indicating that the blood lipids of patients with periodontitis are different from normal levels. It can be seen that dyslipidemia affects the occurrence of periodontitis and may promote the formation of periodontitis in some way. Therefore, clinical patients with dyslipidemia should be vigilant.

This research found that after adjusting for relevant variables, the risk of periodontitis in patients with hyperuricemia was 2.940 times that in those without. High blood uric acid levels can aggravate the inflammatory state of individuals with periodontitis and promote vascular endothelial damage. There is a certain correlation of hyperuricemia with the occurrence and development of periodontitis [13, 14]. Byun et al. [15] analyzed the correlation between periodontitis and serum uric acid level through a cross-sectional study, and the results demonstrated that the serum uric acid level of individuals with periodontitis was higher than that of non-periodontitis sufferers, and that the severity of periodontitis was positively correlated with the increase of blood uric acid. This shows that the increase of blood uric acid is

closely related to periodontitis, and the increase of blood uric acid may be one of the high-risk factors of periodontitis. At the same time, it is not ruled out that periodontitis leads to the increase of serum uric acid.

In epidemiological studies, interaction means that the combined effect of two or more risk factors on the disease is different from the sum or product of their independent effects, that is, additive interaction or multiplicative interaction [16, 17]. The results of this research demonstrated that the risk of periodontitis in patients with dyslipidemia and hyperuricemia was 2.887 times that of those without, and the synergistic effect was 1.485 times that of the sum of the effects of the two alone. Possible mechanisms of the interaction of dyslipidemia and hyperuricemia on periodontitis: high levels of serum uric acid can aggravate the systemic inflammatory state in sufferers with periodontitis, which can further affect the local microenvironment of the periodontitis. The lipotoxicity of dyslipidemia can further interfere with the utilization of insulin in the body and jointly promote the occurrence and development of T2DM and its complication periodontitis [18-20]. Previous studies have shown [21, 22] that the morbidity of hyperuricemia and dyslipidemia in adults in China is at a high level, and there may be a synergistic effect between the two, suggesting that in the early prevention of periodontitis, the control of serum uric acid and blood lipids may be effective.

In conclusion, dyslipidemia and hyperuricemia may have a synergistic effect on periodontitis in patients with T2DM. Improving blood lipids and controlling blood uric acid may synergistically prevent periodontitis in them. However, the limited sample size and scope of this study may lead to a certain bias in the research results, which needs to be further confirmed by a study with broader and more reliable sample size.

Disclosure of conflict of interest

None.

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