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Risk of silent myocardial ischemia detected by single photon emission computed tomography (SPECT) among asymptomatic Chinese patients with type 2 diabetes

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Abstract

To explore the prevalence and risk factors of silent myocardial ischemia (SMI) detected by using single photon emission computed tomography (SPECT) in Chinese asymptomatic patients with type 2 diabetes (T2D).

In this hospital-based retrospective study, 821 T2D patients who were screened for SMI detected by stress myocardial perfusion imaging using SPECT between June 2014 and July 2016 were investigated. Clinical indicators were compared between the patients with SMI and controls without SMI. Risk factors for SMI were evaluated by univariate and multivariate analysis.

In this study, there were 131 patients with SMI in asymptomatic diabetes and the prevalence of SMI was 21.3% of 614 individuals. Logistic regression analysis indicated that diabetic retinopathy (OR = 1.474, 95%CI: 1.113–1.951, $P = .007$), male gender (OR = 1.805, 95%CI: 1.183–2.747, $P = .006$), and low-density lipoprotein (LDL) cholesterol (OR = 1.298, 95%CI: 1.042–1.615, $P = .02$) were risk factors associated with SMI. Besides, the prevalence of SMI increased in associated with the progression of retinopathy ($P = .041$). The percentage of SMI diagnosed in patients with no diabetic retinopathy (NDR), non-proliferative diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR) were 18.5% (75/405), 25.2% (37/147), and 30.6% (19/62), respectively. The percentage of SMI in male (24.5%, 85/347) was higher than that in female (17.2%, 46/267), $P = .029$.

Physicians should be aware of these conditions when examining male patients with type 2 diabetes, especially with DR and/or high level of low-density lipoprotein cholesterol (LDL cholesterol), even if otherwise asymptomatic. A routine screening for SMI may thus be considered advisable in these patients.

Abbreviations: BMI = body mass index, DBP = diastolic blood pressure, LDL cholesterol = low-density lipoprotein cholesterol, MPI = myocardial perfusion imaging, NDR = no diabetic retinopathy, NPDR = non-proliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy, SBP = systolic blood pressure, SMI = silent myocardial ischemia, SPECT = single photon emission computed tomography, T2D = type 2 diabetes, TC = total cholesterol, TG = triglyceride, UAER = urinary albumin excretion rate.

Keywords: diabetes, diabetic retinopathy, silent myocardial ischemia, SPECT

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This is the first work to evaluate the prevalence and risk factors of silent myocardial ischemia (SMI) detected stress myocardial perfusion imaging using technetium-99m-methoxy-isobutyl-isonitrile single-photo emission computed tomography (SPECT) in Chinese asymptomatic type 2 diabetes. This research complements an earlier study which found that physicians should be aware of these conditions when examining male patients with type 2 diabetes, especially with diabetic retinopathy and/or high level of low-density lipoprotein cholesterol.

X-RZ and H-rZ were contributed equally to this work.

All of the authors gave their consent to the publication.

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The datasets used and analyzed during the current study are available from the corresponding author (YJK) upon reasonable request.

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1. Introduction

Coronary artery disease, a severe macrovascular complication among patients with type 2 diabetes (T2D), is often asymptomatic in patients with diabetes until the onset of myocardial infarction or sudden cardiac death.[1] Indeed, silent myocardial ischemia (SMI) can be detected on average in 26% of asymptomatic diabetes, exposing them to a 3.5-fold increased risk of cardiac events.[2] Therefore, early identification of SMI in the diabetic population is needed.

Silent myocardial ischemia in asymptomatic patients with type 2 diabetes can be detected by stress myocardial perfusion imaging (MPI) using single-photo emission computes tomography (SPECT). It is still under debate which patients with T2D should be tested for SMI. The American Diabetes Association (ADA) suggested that T2D patients with two or more risk factors including hyperlipidemia, hypertension, active smoking, and albuminuria were recommended to screen for SMI.[3] However, guidelines developed in the United States were often not applicable in Asian countries because of differences in body habitus, healthcare systems and disease prevalence between Asian and Western countries. Nevertheless, there were sporadic researches conducted in Asian populations. Therefore, it is necessary to identify the most relevant risk factors associated with SMI in Chinese T2D populations.

This investigation is the first to explore the risk factors of SMI detected by using SPECT in Chinese asymptomatic T2D patients.

2. Methods

2.1. Subjects

The patients were recruited from the Department of Diabetology of Tongren hospital (Beijing, China) between June 2014 and July 2016. Eligibility criteria including type 2 diabetes who were screened with stress myocardial perfusion imaging using SPECT. Exclusion criteria were as follows:

1. history of known coronary artery disease, congenital heart disease or known cardiomyopathy, or any clinical indication for stress testing;
2. limited life expectancy or end-stage renal or liver disease.

All of the participants' medical histories were obtained and the patients received a physical examination, including age, sex, duration, smoking habit, blood pressure, body mass index (BMI), ECG. Meanwhile, they underwent blood and urine laboratory testing.

2.2. Screening for SMI and stress myocardial perfusion imaging

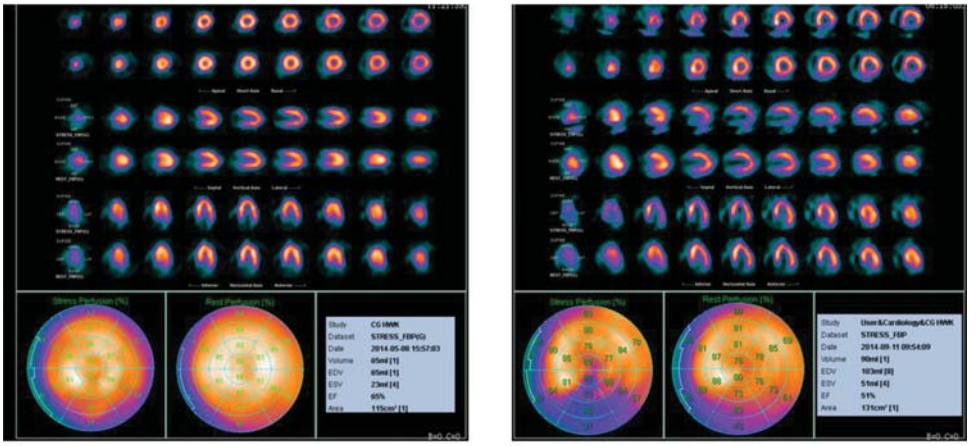
All of the patients were systematically screened with stress myocardial perfusion imaging using SPECT to evaluate the myocardial ischemia. For stress SPECT, adenosine (Adenoscan, Astellas Pharma US, Inc., Deerfield, IL) was infused over 6 minutes at 140 μg/kg/min and Tc-99m sestamibi was injected at 3.05 ± 0.4 minutes of adenosine infusion, and stress images were acquired within 15 to 60 minutes. SMI was defined as detection of perfusion abnormalities by stress MPI using SPECT.[4] Representative images of normal and reversible defect myocardial perfusion SPECT in type 2 diabetic subject were observed in Figure 1.

2.3. Assessment of DR grading

The presence of DR was diagnosed using digital retinal photographs (2 eyes × 2 fields), taken by using a TRC-NW7SF (Topcon Co. Tokyo, Japan) non mydriatic camera at 45°. These photographs were subsequently examined independently by 2 qualified retinal photography graders in accordance with quality assurance protocols. The severity of DR was graded based on the international clinical diabetic retinopathy and diabetic macular edema disease severity scale.[5] Diabetic retinopathy was classified into 5 grades:

1. no retinopathic changes;
2. mild non-proliferative retinopathy (NPDR);
3. moderate NPDR;
4. severe NPDR; and
5. proliferative retinopathy (PDR).

The degree of diabetic retinopathy was determined according to the grading in the worse eye.



A B

Figure 1. Images corresponding to myocardial perfusion SPECT obtained in SMI and non-SMI subjects. (A) Normal SPECT in a representative patient with type 2 diabetes. (B) Reversible defect in the left ventricular apical third of the anterior, septal and lateral region in a representative patient with type 2 diabetes with SMI. SMI = silent myocardial ischemia, SPECT = single photon emission computed tomography.

2.4. Ethical statement

The study was conducted with the approval from the Ethics Committee of Beijing Tongren Hospital, Capital Medical University, and adhered to the *Declaration of Helsinki*. Written informed consent was obtained from each participant.

2.5. Statistical analysis

Continuous variables with normal distribution were presented as mean ± standard derivation (SD). If continuous variables had a skewed distribution, the median and interquartile range of the variable was used. Normally distributed data were analyzed by *t* test, while nonnormally distributed data were compared using the rank-sum test. Categorical data were compared by the χ^2 test. Multivariate analysis was performed using the logistic regression method. Statistical analysis was performed using SPSS 17.0 (SPSS Inc, Chicago, IL). All of the statistical tests were 2-sided and considered statistically significant if $P < .05$.

3. Results

3.1. Patient characteristics and laboratory analysis

In this hospital-based cross-sectional study, of the 821 eligible participates, 207 participants were excluded because of meeting exclusion criteria. A final total of 614 participants were included in this research (Fig. 2).

In all of the patients, the average age was 57.0 ± 10.8 years and the duration of diabetes was 10.9 ± 7.6 years. The value of the hemoglobin A1c (HbA1c) was 8.9 ± 2.0%. Besides, the prevalence of DR and albuminuria was 34% (209/614) and 27.5% (165/614).

Then diabetic patients were divided into 2 groups with and without SMI. A total of 131 (21.3%) patients with type 2 diabetes suffered from SMI detected by using SPECT. No significant differences were found in duration of known diabetes, age, blood pressure, smoke history, BMI, total cholesterol (TC), triglyceride (TG), LDL, and HDL cholesterol, except for gender, albuminuria, and stage of DR (Table 1). The trend to severe retinopathy and nephropathy in the SMI group was significantly higher than that in the non-SMI group ($P < .05$).

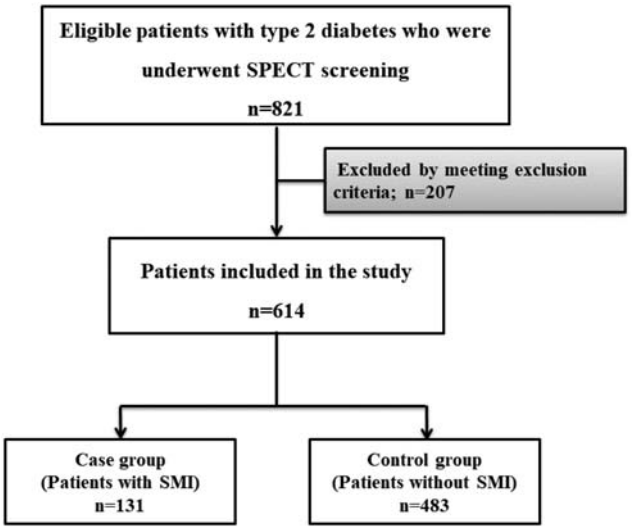


Figure 2. Selection of patients for study. A total of 821 patients with type 2 diabetes were investigated by using SPECT, and 614 participants were included in the analysis. SPECT = single photon emission computed tomography.

Table 1

Baseline demographics in the study.

	Total	SMI	No SMI	*P* value
n	614	131	483	–
Age (yr)	57.0 ± 10.8	56.0 ± 10.6	57.3 ± 10.8	.234
Gender (Male/Female)	347/267	85/46	262/221	.029*
Diabetes duration (yr)	10.9 ± 7.6	10.0 ± 7.2	11.1 ± 7.7	.156
Smoke	247 (40.2%)	62 (47.3%)	185 (38.3%)	.062
DR	209 (34.0%)	56 (42.8%)	153 (31.7%)	.013*
BDR	147	37	110	
PDR	62	19	43	
BMI (kg/m^2)	25.83 ± 3.59	25.92 ± 3.41	25.81 ± 3.63	.770
SBP (mmHg)	133.0 ± 18.7	135.7 ± 17.0	132.3 ± 19.0	.065
DBP (mmHg)	77.2 ± 11.5	78.4 ± 11.1	76.9 ± 11.6	.187
Cr (umol/L)	70.7 ± 25.0	73.6 ± 25.2	69.9 ± 25.0	.134
TG (mmol/L)	2.0 ± 1.4	2.1 ± 1.5	1.9 ± 1.3	.149
TC (mmol/L)	4.6 ± 1.1	4.7 ± 1.2	4.5 ± 1.1	.080
LDL-c (mmol/L)	2.8 ± 1.0	2.9 ± 1.0	2.8 ± 0.9	.082
HDL-c (mmol/L)	1.0 ± 0.4	1.0 ± 0.4	1.0 ± 0.4	.231
FBG (mmol/L)	8.1 ± 2.8	8.3 ± 2.7	8.0 ± 2.8	.280
HbA1c (%)	8.9 ± 2.0	8.9 ± 2.0	9.0 ± 2.0	.702
Albuminuria	165 (27.5%)	43 (34.4%)	122 (30.0%)	.038†,*
Microalbuminuria (UAER 20–200 ng/ml)	110	25	85	
Macroalbuminuria (UAER > 200 ng/ml)	55	18	37	

Data are mean±SD or median (25th, 75th interval) unless otherwise indicated.

Cr = creatinine, DBP = diastolic blood pressure, HDL-C = HDL cholesterol, LDL-C = LDL cholesterol, SBP = systolic blood pressure, SMI = silent myocardial ischemia, TC = total cholesterol, TG = triglyceride, UAER = urinary albumin excretion rate.

† Rank sum test.

* $P < .05$, No-SMI vs SMI group.

Table 2

Logistic regression analysis of silent myocardial ischemia (SMI) associated factors.

Independent variable	OR	95% Confidence interval	*P*
DR	1.474	1.113–1.951	.007**
Gender (Male)	1.805	1.183–2.747	.006**
LDL-c	1.298	1.042–1.615	.02*

* $P < .05$.
** $P < .01$.

3.2. Risk factors for SMI

Logistic regression analysis was applied, where the variables were selected because they were associated with the presence of SMI with a *P* value < .10 (male gender, smoke, DR, albuminuria, TC, LDL-c, SBP). It indicated that diabetic retinopathy (OR = 1.474, 95%CI: 1.113–1.951, *P* = .007), male gender (OR = 1.805, 95% CI: 1.183–2.747, *P* = .006), and low-density lipoprotein (LDL) cholesterol (OR = 1.298, 95%CI: 1.042–1.615, *P* = .02) were independent risk factors associated with SMI. The results were shown in Table 2.

3.3. Prevalence of SMI according to the stage of DR, male

As shown in Fig. 3, the prevalence of SMI increased in associated with the progression of retinopathy (*P* = .041). The percentage of SMI diagnosed in patients with no diabetic retinopathy (NDR), non-proliferative diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR) were 18.5% (75/405), 25.2% (37/147), and 30.6% (19/62), respectively. Besides, the percentage of SMI in male (24.5%, 85/347) was higher than that in female (17.2%, 46/267), *P* = .029.

4. Discussions

In this study, we have evaluated the prevalence and risk factors of silent myocardial ischemia detected by using SPECT in Chinese asymptomatic patients with type 2 diabetes. And concluded that Chinese male patients with type 2 diabetes with retinopathy and high levels of LDL-cholesterol are at increased risk of silent myocardial ischemia. Patients of T2DM with SPECT-detected SMI had significantly higher risks of cardiac death, all-cause mortality, nonfatal cardiac events and total cardiac events compared to patients without SMI.[2] Cardiovascular neuropathy, affecting myocardial sympathetic and parasympathetic fibers, is one of the mechanisms responsible for the increased incidence of SMI in these patients. Obviously, a significant proportion of diabetic patients with no clinical evidence for coronary artery disease are suffering from SMI and are at great risk for cardiovascular events. The prevalence of SMI reported in previous studies was highly variable, ranging from 11% to 50%.[6–8] The prevalence of SMI in our study was 23.1% of 614 patients. It was consistent with DIAD study which showed myocardial perfusion deficit in 22% of 522 patients.[9]

Screening for SMI in patients is intuitively attractive as this might potentially lead to benefits. But the utility of screening patients with type 2 diabetes for SMI is controversial. Recently, in the DIAD study[9] it was observed that the rates of cardiac events were not reduced by MPI screening for SMI. Actually, only 4.4% of participants underwent coronary angiography and 9 participants underwent early revascularization, which might interfere with the incidence of cardiovascular events between the 2 groups. The COURAGE subgroup study, moreover, suggested that T2D patients will benefit from silent myocardial ischemia screening, especially patients who accepted early revascularization.[10] However, routine screening of asymptomatic patients with diabetes would be prohibitively expensive, so it is necessary to identify the most relevant risk factors associated with SMI.

Actually, the risk factors for SMI remained controversial in former studies. The Framingham Heart Study[11,12] has identified hyper LDL-c, diabetes. Hypertension and smoking were found to be relevant risk factors for SMI. The DIAD study[9] found autonomic dysfunction, maleness, and duration of diabetes to be the most important predictors of SMI. In Asian populations, the Japan Diabetes Complication Study showed that age, maleness, and LDL-c level were risk factors for ischemic heart disease.[13] However, this is the first work to evaluate the risk factors of SMI detected stress MPI using SPECT in Chinese asymptomatic type 2 diabetes. In this study, we evaluated the risk factors of SMI in a Chinese T2D population. It indicated that diabetic retinopathy

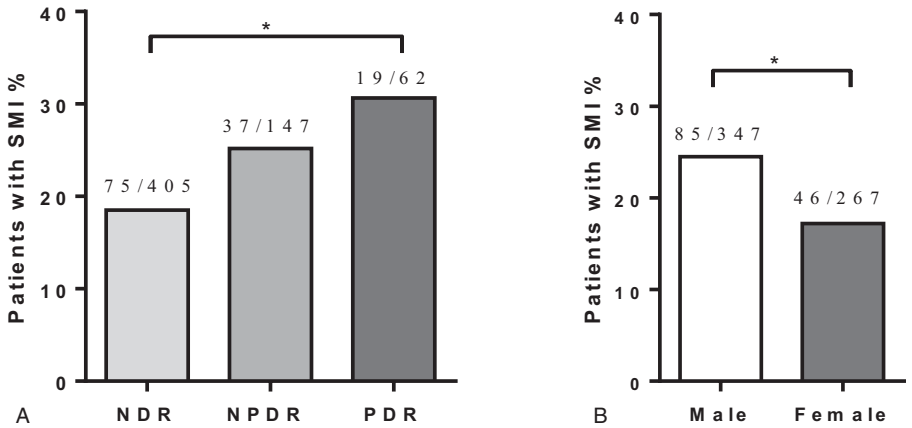


Figure 3. The prevalence of SMI in the different groups. (A) The prevalence of SMI increased in associated with the progression of retinopathy. The prevalence of SMI diagnosed in NDR, NPDR, and PDR patients were 18.5% (75/405), 25.2% (37/147), and 30.6% (19/62), respectively. (B) The prevalence of SMI diagnosed in male and female patients group were 24.5% (85/347) and 17.2% (46/267). *$P < .05$. NDR = no detectible diabetic retinopathy, NPDR = non-proliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy, SMI = silent myocardial ischemia.

(OR = 1.474, 95%CI: 1.113–1.951, $P = .007$), male gender (OR = 1.805, 95%CI: 1.183–2.747, $P = .006$), and low-density lipoprotein (LDL) cholesterol (OR = 1.298, 95%CI: 1.042–1.615, $P = .02$) were independent risk factors associated with SMI. Meanwhile, maleness and LDL-c were already acknowledged traditional risk factors of SMI. Thus, taking into account retinopathy status might further improve the selection of patients for SMI screening.

Our study suggested that T2D patient with diabetic retinopathy, a typical microvascular complication of diabetes, more likely to suffer from SMI. Diabetic retinopathy has previously been found to be associated with CHD.[7,13–15] A recent population-level cohort study[16] also found that microvascular disease significantly affected the risk of future cardiovascular disease among individuals with type 2 diabetes. The possible explanation was that micro and macrovascular complications of diabetes share common pathogenic mechanisms, including endothelial dysfunction, oxidative stress, inflammation.[15,17–20] An alternative mechanism was that DR might reflect myocardial microvascular disease. The cause of SMI might be related solely to coronary artery disease but also myocardial microangiopathy.[21] For all these reasons, T2D patients with DR present a higher risk suffering from SMI. However, our findings were based on this cross-sectional study. Further follow-up of the patients is needed regarding the clinical prognosis data of this study. We wish to make a breakthrough in this research field.

5. Limitations

To our knowledge there have been no relevant studies evaluating risk factors of SMI diagnosed with SPECT in Chinese T2D patients. However, stratified analysis was not made according to the degree of myocardial ischemia. Besides, this study cannot explain why patients with type 2 diabetes with DR had a high risk of SMI. A large clinical trial with a long follow-up period may provide evidence to support screening of SMI in these patients. Finally, this was a single center study, with the possibility of selection bias. Therefore, further multicenter, prospective studies are warranted to confirm our findings.

6. Conclusion

Within the Chinese population, male patients with type 2 diabetes with DR and high levels of LDL cholesterol are at an increased risk of SMI. A routine screening for SMI may thus be considered advisable in these patients.

Author contributions

JKY and XRZ contributed to the design of the study, analysis, and interpretation of data, and prepared all of the figures and tables. JKY, XRZ, and HRZ, drafted a portion of the manuscript. JBZ, ML, ZZ, WL, and GRY took part in analyzing data and drafting a portion of the manuscript. All of the authors reviewed the manuscript.

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References

[1] Cheung N, Wang JJ, Klein R, et al. Diabetic retinopathy and the risk of coronary heart disease: the atherosclerosis risk in communities study. Diabetes Care 2007;30:1742–6.
[2] Zhang L, Li H, Zhang S, et al. Silent myocardial ischemia detected by single photon emission computed tomography (SPECT) and risk of cardiac events among asymptomatic patients with type 2 diabetes: a meta-analysis of prospective studies. J Diabetes Complications 2014;28:413–8.
[3] Consensus development conference on the diagnosis of coronary heart disease in people with diabetes: 10–11 February 1998, Miami, Florida. American Diabetes Association. Diabetes Care 1998;21:1551–9.
[4] Mulvagh SL, DeMaria AN, Feinstein SB, et al. Contrast echocardiography: current and future applications. J Am Soc Echocardiogr 2000;13:331–42.
[5] Wilkinson CP, Ferris FL, 3rd , et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1677–82.
[6] Bax JJ, Bonow RO, Tschope D, et al. Global Dialogue Group for the Evaluation of Cardiovascular Risk in Patients with D. The potential of myocardial perfusion scintigraphy for risk stratification of asymptomatic patients with type 2 diabetes. J Am Coll Cardiol 2006;48:754–60.
[7] Hernandez C, Candell-Riera J, Ciudin A, et al. Prevalence and risk factors accounting for true silent myocardial ischemia: a pilot case-control study comparing type 2 diabetic with non-diabetic control subjects. Cardiovasc Diabetol 2011;10:9.
[8] Araz M, Celen Z, Akdemir I, et al. Frequency of silent myocardial ischemia in type 2 diabetic patients and the relation with poor glycemic control. Acta Diabetol 2004;41:38–43.
[9] Young LH, Wackers FJ, Chyun DA, et al. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study, a randomized controlled trial. JAMA 2009;301:1547–55.
[10] Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation 2008;117:1283–91.
[11] Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. Circulation 1979;59:8–13.
[12] Fox CS. Cardiovascular disease risk factors, type 2 diabetes mellitus, and the Framingham Heart Study. Trends Cardiovasc Med 2010;20:90–5.
[13] Sone H. Clinical and pathophysiological features of Japanese patients with type 2 diabetes mellitus and their risk factors for diabetic complication. Nihon Rinsho 2015;73:1979–87.
[14] Janand-Delenne B, Savin B, Habib G, et al. Silent myocardial ischemia in patients with diabetes: who to screen. Diabetes Care 1999;22:1396–400.
[15] Ohtomo K, Shigeeda T, Hirose A, et al. Silent myocardial ischaemia in patients with diabetic retinopathy. Acta Ophthalmol 2014;92:e492–3.
[16] Brownrigg JR, Hughes CO, Burleigh D, et al. Microvascular disease and risk of cardiovascular events among individuals with type 2 diabetes: a population-level cohort study. Lancet Diabetes Endocrinol 2016;4:588–97.
[17] Hammes HP. Diabetic retinopathy: hyperglycaemia, oxidative stress and beyond. Diabetologia 2018;61:29–38.
[18] Cheung N, Wong TY. Diabetic retinopathy and systemic vascular complications. Prog Retin Eye Res 2008;27:161–76.
[19] Klein R, Klein BE, Moss SE, et al. Retinal vessel caliber and microvascular and macrovascular disease in type 2 diabetes: XXI: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Ophthalmology 2007;114:1884–92.
[20] Zhu XR, Zhang YP, Bai L, et al. Prediction of risk of diabetic retinopathy for all-cause mortality, stroke and heart failure: Evidence from epidemiological observational studies. Medicine (Baltimore) 2017;96:e5894.
[21] Um T, Lee DH, Kang JW, et al. The degree of diabetic retinopathy in patients with type 2 diabetes correlates with the presence and severity of coronary heart disease. J Korean Med Sci 2016;31:1292–9.