HbA1c Independently Predicts Declined Myocardial Perfusion Reserve Index in Patients With Coronary Microvascular Disease Using Stress Perfusion Cardiac Magnetic Resonance: an Observational Study

Jingwen Yong

Beijing Anzhen Hospital, Capital Medical University

JinFan Tian

Beijing Anzhen Hospital, Capital Medical University

JiaXin Cao

Beijing Friendship Hospital, Capital Medical University

HuiHui Kong

Beijing Friendship Hospital, Capital Medical University

Xin Zhao

Beijing Anzhen Hospital, Capital Medical University

XueYao Yang

Beijing Anzhen Hospital, Capital Medical University

Yi He

Beijing Friendship Hospital, Capital Medical University

Xiantao Song (✉ songxiantao0929@qq.com)

Beijing Anzhen Hospital, Capital Medical University <https://orcid.org/0000-0002-2114-2230>

Original investigation

Keywords: HbA1c, myocardial perfusion reserve index, coronary microvascular disease, stress perfusion cardiac magnetic resonance, diabetes

Posted Date: August 24th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-814521/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background

We investigated whether glycated haemoglobin A1c (HbA1c) could independently predict the decline in the myocardial perfusion reserve index (MPRI) in patients with coronary microvascular disease (CMD) by stress perfusion cardiac magnetic resonance (CMR).

Methods

From November 2019, 174 patients with ischemic symptoms but without obstructive coronary disease were screened. The MPRI was recorded in 88 patients who underwent stress perfusion CMR detection. Eighty patients with an MPRI of < 2.5 were included in the study. The patients were divided into two groups based on whether their MPRI was greater or less than 1.47. The effects of each index on the MPRI were analysed using bivariate correlation analysis, and the risk factors for CMD were explored using logistic regression analysis.

Results

A total of 80 patients with an MPRI of 1.69 ± 0.79 were included (mean age 54.07 ± 11.06 years; 66.3% male). CMD patients with an MPRI of ≤ 1.47 were higher than those in the group with an MPRI of > 1.47 in age (57.61 ± 9.65 years vs. 51.74 ± 11.41 years), presence of diabetes mellitus (45.5% vs. 21.3%), fasting blood glucose levels [$6.33(5.16, 8.01)$ vs. $5.30(5.15, 6.56)$], and HbA1c levels [$6.30(5.70, 7.70)$ vs. $5.80(5.60, 6.50)$], ($P < 0.05$). The MPRI was negatively correlated with HbA1c ($r = -0.378$, $P = 0.004$). Logistic regression analysis showed that HbA1c (OR=2.336, 95% CI: 1.119-4.876, $P = 0.024$) was an independent risk factor for decreased MPRI in all patients with CMD, especially in patients without diabetes (OR=19.953, 95% CI: 1.743-93.449, $P = 0.029$), but not in patients with diabetes (OR=0.984, 95% CI: 0.265-3.658, $P = 0.981$).

Conclusions

HbA1c is an independent predictor of MPRI decline in CMD patients, notably in CMD patients without diabetes, but not for those with diabetes.

Trial Registration

This clinical trial has been registered in the Chinese clinical Trial Registry with an identifier: ChiCTR1900025810.

Background

Coronary artery microvascular disease (CMD) is a health issue of great concern¹. Up to 50%-65% of patients with stable chest pain and non-obstructed coronary arteries are considered to have CMD², which leads to reduced diastolic function and a poor prognosis^{3,4}. The main pathological process of angina caused by CMD is impaired microvascular blood flow reserve or load-induced microvascular spasm, resulting in the inability of the microvasculature to expand to maintain normal myocardial perfusion⁵.

Currently, the approaches for myocardial microcirculation function evaluation are limited, and the commonly used non-invasive methods depend on detecting the segmental difference of left ventricular (LV) perfusion or segmental motion abnormalities (such as single-photon emission computerized tomography, positron emission tomography, cardiac magnetic resonance (CMR), or stress echocardiography)¹. Stress perfusion CMR can quantify myocardial

perfusion and is now a very mature non-invasive technique for evaluating CMD. The myocardial perfusion reserve index (MPRI) measured by CMR is a robust semi-quantitative imaging index that represents the vasodilation capacity of small vessels. It is defined as the standardised ratio of stress/rest LV rise of the blood pool ^{6,7}. A recent study found that in patients with CMD, the incidence of major adverse cardiovascular events (MACEs) in patients with an MPRI of ≤ 1.47 was three times higher than that in patients with an MPRI of > 1.47 ⁸.

HbA1c is the gold indicator of blood glucose control, which can reflect the average level in the past 2–3 months⁹. HbA1c is an independent predictor of cardiovascular outcomes ¹⁰ as blood glucose control is closely related to cardiovascular disease ^{11,12}. For each percentage unit of HbA1c, the incidence of cardiovascular and microvascular events can increase by 18%, and 30%, respectively¹³. Intensive blood glucose control (reducing HbA1c to $< 6.5\%$) can reduce major microvascular events but cannot reduce cardiovascular events ¹⁴. A previous study revealed that the mean HbA1c was higher in CMD patients than in non-CMD patients¹⁵; however, whether HbA1c could independently predict a decline in MPRI remains unclear.

This study aimed to detect the MPRI in patients with CMD by stress perfusion CMR, analyse the correlation between HbA1c and MPRI, and determine whether HbA1c is an independent risk factor for a declined MPRI.

Methods

Study population and database

The diagnostic criteria of CMD referred to the expert consensus of the European Association for Percutaneous Cardiovascular Intervention and the European Society for Cardiology ¹. The inclusion criteria included: aged 18–80 years, with typical angina symptoms but with no coronary stenosis or mild stenosis (stenosis $< 50\%$) as confirmed by invasive coronary angiography (ICA)/coronary computed tomography angiography (CCTA), and an MPRI of < 2.5 . The exclusion criteria included: allergy to imaging agents; claustrophobia; obstructive coronary heart disease, coronary spasm, acute myocarditis, pericarditis, cardiomyopathy, myocardial bridge, high atrioventricular block, and angina pectoris caused by recent acute myocardial infarction; acute systemic diseases or infections, severe liver and kidney dysfunction, and uncontrolled metabolic diseases; pregnant and lactating women; asthma; and pacemaker, metal ossicles, knee joints, and other metals that cannot be examined by CMR. Due to the large inter-population variability of the MPRI, in order to reduce statistical errors, we divided patients into two groups according to a reference¹⁶ using an MPRI ≤ 1.47 as the standard. A flowchart of the study is shown in Fig. 1.

Study design

The following data was collected: basic patient information (age, gender, height, and weight); medical history (smoking, previous myocardial infarction history, previous percutaneous coronary intervention [PCI] treatment history, hypertension, hyperlipidaemia, diabetes mellitus, and family history of coronary artery disease); basic vital signs (blood pressure and heart rate); laboratory tests (peripheral white blood cells [WBC], high-sensitivity C-reactive protein, complement C1q, NT-proBNP, creatine kinase isoenzyme MB [CK-MB], cardiac troponin I [cTnI], D-Dimer, fasting blood glucose [FBG], glycosylated haemoglobin [HbA1c], total cholesterol [TC], triacylglycerol [TG], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], uric acid [UA], and homocysteine [HCY]); results of echocardiography (left ventricular ejection fraction [LVEF], E/A, and LV diastolic dysfunction); symptoms; angina classification of the Canadian Cardiovascular Society (CCS), Seattle Angina Quality of Life Score (SAQ), Patient Health Questionnaire-9 (PHQ-9), and Generalized Anxiety Disorder Questionnaire-7 (GAD-7). Overweight was defined

as a body mass index (BMI) of > 24. Risk factors were defined as a combination of smoking, hypertension, diabetes, hyperlipidaemia, obesity, and a family history of coronary heart disease.

Stress perfusion CMR image acquisition

Patients were fasted for 6–8 hours before the CMR examination. It is forbidden to drink tea and coffee, and take β -blockers, vasoactive drugs, and theophylline drugs 24 hours before the examination. The inspection was conducted using a 3.0 T scanner (Magenetom PRISMA, Siemens, Erlangen, Germany). The patients were placed in the supine position, using electrocardiogram gating and 32-channel phased-array coils to detect heart rate/rhythm and respiration. The standardised imaging protocol included cardiac movies (4-chamber, 2-chamber, 3-chamber, 8–10 short-axis views of the LV from the basal segment to the apex of the heart), stress perfusion (4-chamber view, 3 LV short-axis: basal section, central section, and apical section), resting perfusion (the scanning section is the same as stress perfusion), and late gadolinium-enhanced (the scanning section is the same as stress perfusion). Dual venous access was established before examination. Using adenosine triphosphate (ATP) as the first-pass vasodilator, one side was chosen to inject 0.16 mg/(min*kg) of ATP at a constant rate for more than 5 minutes to achieve a full load. The patient's vital signs were monitored before and after ATP injection and throughout the process. In the first 4 min of ATP injection, a dose of 0.15 mmol/kg of Gd DTPA (Magnevist, Bayer Schering, Germany) was injected through the contralateral venous channel at a flow rate of 4 ml/s. Ten minutes after the completion of the stress perfusion scan, a late gadolinium-enhanced scan was performed. Fifteen minutes after the completion of the stress perfusion, a resting perfusion scan was performed, with only a bolus injection of contrast agent, and the injection rate and dose were the same as in the stress perfusion scan.

Stress perfusion CMR imaging analysis

Clinical diagnosis and parameters of cardiac function were obtained from the CMR reports. Circle CVI42 (Circle Cardiovascular Imaging Inc. Canada) was used to evaluate the MPRI. In the perfusion module, both the stress and rest perfusion images were loaded. Doctors with extensive CMR reading experience manually drew the epicardium and endocardium and blood pool marks on every cardiac phase of the basal, middle, and apical slices. A section of the LV blood pool is central, avoiding the LV papillary muscles. The insertion points were marked at the junction of the left and right anterior walls (Fig. 2). It was then learned and expanded through artificial intelligence to automatically generate the signal intensity curve of the segmental myocardium and the LV blood pool (Fig. 2). The global MPRI was calculated as the average of all 16 segments. An MPRI of ≥ 2.5 was defined as the normal value¹ and an MPRI cutoff value of ≤ 1.47 was shown to be significant in predicting patient outcomes¹⁶.

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation (normal distribution) or medians and interquartile range (IQR), while categorical variables are presented as numbers (%). The t-test or rank sum test was used to compare the differences between groups of continuous variables. The chi-square test was used to compare groups of categorical variables. The correlation between the MPRI and various risk factors was determined using Pearson/Spearman correlation analysis. The meaningful variables in univariate analysis and correlation analysis, PHQ-9, and GAD-7 scores were independent variable and the dependent variable was whether the MPRI was > 1.47. A logistic regression analysis was performed, and the effect value was expressed as an odds ratio (OR). In addition, we performed a logistic regression analysis separately for patients without diabetes. Statistical significance was set at $p < 0.05$. All statistical analysis was performed using SPSS19.0 software.

Results

Patient cohort

From November 2019 to July 2021, we screened a total of 174 patients who were hospitalised or outpatients in the first ward of the Department of Cardiology of Beijing Anzhen Hospital due to ischemic symptoms and had confirmed nonobstructive coronary arteries by CCTA or ICA. The MPRI was achieved in 88 patients who underwent stress-perfusion CMR. Finally, 80 patients with an MPRI of < 2.5 were analysed.

The average age was 54 years (54 ± 14 years), and 66.3% were males. Forty-eight (60%) and 32 (40%) patients underwent CCTA and ICA, respectively, confirming the presence of nonobstructive coronary arteries. The flow chart in Fig. 1 provides further details.

Patient characteristics

The clinical characteristics of the patients are summarised in Table 1. Age (57.61 ± 9.65 vs. 51.74 ± 11.41) and presence of diabetes mellitus (45.5% vs. 21.3%) in the group with an MPRI of ≤ 1.47 were higher than the MPRI of > 1.47 group ($P < 0.05$). There were no significant differences in gender, being overweight, smoking, heart rate, blood pressure, myocardial infarction history, PCI history, hypertension, and hyperlipidaemia between the two groups ($P > 0.05$).

Table 1
Patients Characteristic

	MPRI ≤ 1.47	MPRI > 1.47	P value
N	33	47	
Age	57.61 ± 9.65	51.74 ± 11.41	0.006*
Gender(male)	20(60.6%)	32(68.1%)	0.478
Overweight	23(69.7%)	30(63.8%)	0.637
Smoking	9(27.2%)	21(44.7%)	0.160
Vital signs			
Heart rate	70.81 ± 6.92	71.89 ± 8.94	0.566
SBP	127.64 ± 12.88	128.20 ± 17.91	0.768
DBP	75.18 ± 7.56	78.20 ± 11.66	0.313
Comorbidity			
MI history	4(12.1%)	5(10.6%)	0.837
PCI history	7(21.2%)	8(17.0%)	0.773
Hypertension	21(63.6%)	23(52.3%)	0.255
Dyslipidemia	17(51.5%)	25(53.2%)	0.883
Diabetes mellitus	15(45.5%)	10(21.3%)	0.022*
No risk factors	8(24.2%)	11(23.4%)	0.931
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction; PCI, percutaneous coronary intervention. *p < 0.05			

Table 2
Laboratory examination

	MPRI $\leq$ 1.47	MPRI $>$ 1.47	P value
WBC($\times 10^9$ /L)	6.84 $\pm$ 1.97	6.80 $\pm$ 1.75	0.930
hs-CRP (mg/l)	0.64(0.34,4.33)	0.65(0.45,1.52)	0.832
C1q (mg/l)	146.19(130.10,157.19)	146.30(131.85,178.15)	0.804
NT-pro BNP (pg/ml)	60.30(29.05,78.60)	61.60(42.15,115.55)	0.945
CK-MB (ng/ml)	1.90(1.00,2.90)	1.70(1.50,2.10)	0.586
cTnl(ng/ml)	2.70(0.10,7.05)	2.70(0.22,5.25)	0.598
D-Dimer (ng/ml)	79.50(50.50,109.25)	54.00(30.50,81.00)	0.056
FBG (mmol/l)	6.33(5.16,8.01)	5.30(5.15,6.56)	0.035*
HbA1c (%)	6.30(5.70,7.70)	5.80(5.60,6.50)	0.004*
TC (mmol/l)	3.76 $\pm$ 0.84	3.88 $\pm$ 1.05	0.861
TG (mmol/l)	1.32(1.16,1.62)	1.26(0.98,1.51)	0.454
LDL-C (mmol/l)	2.11 $\pm$ 0.73	2.16 $\pm$ 0.85	0.870
HDL-C (mmol/l)	1.12 $\pm$ 0.25	1.14 $\pm$ 0.33	0.953
UA(μ mol/L)	361.18 $\pm$ 106.619	303.38 $\pm$ 91.071	0.020*
HCY	11.85(10.30,15.10)	11.75(10.12,13.50)	0.413
Echocardiography			
LVEF	59.94 $\pm$ 15.39	63.75 $\pm$ 6.95	0.476
E/A	0.95 $\pm$ 0.37	1.00 $\pm$ 0.33	0.449
LV diastolic dysfunction	20(90.9%)	16(69.6%)	0.135
WBC, white blood cells; hsCRP, high-sensitivity C-reactive protein; C1q, complement C1q; NT-pro BNP, NT- B type natriuretic peptide; CK-MB creatine kinase isoenzyme MB; cTnl, cardiac troponin I; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triacylglycerol; LDL-C, Low Density Lipoprotein Cholesterol; HDL-C, High density lipoprotein cholesterol; UA, uric acid; HCY, Homocysteine; LVEF, left ventricular ejection fraction; LV, left ventricular. *p<0.05			

Laboratory examination

FBG [6.33(5.16,8.01) vs. 5.30(5.15,6.56)], HbA1c [6.30(5.70,7.70) vs. 5.80(5.60,6.50)] and UA (361.18 $\pm$ 106.619 vs. 303.38 $\pm$ 91.071) in the group with an MPRI of $>$ 1.47 were higher than the MPRI of $\leq$ 1.47 group. There were no

significant differences in inflammatory indices (WBC, hs-CRP, and C1q), myocardial injury markers (NT-pro BNP, CK-MB, cTnI, and D-dimer), blood lipids (TC, TG, LDL-C, and HDL-C), HCY, and echocardiographic indices (LVEF, E/A, and LV diastolic dysfunction) between the two groups.

Symptoms and psychological assessment

There was no significant difference in the classification of angina (typical, exercise, rest, evening angina, and breathlessness) and the degree of angina (CCS classification and SAQ) between the two groups (Supplementary Table 1). There was also no significant difference in the PHQ-9 and GAD-7 scores (Supplementary Table 2).

Correlation analysis and logistic regression of MPRI with risk factors

In patients with CMD, the MPRI was negatively correlated with age ($r=-0.349$, $P=0.001$), diabetes mellitus ($r=-0.324$, $P=0.003$), HbA1c ($r=-0.378$, $P=0.004$), UA ($r=0.311$, $P=0.008$), and HCY ($r=0.246$, $P=0.048$). The MPRI was not correlated with age, FBG, LVEF, E/A, PHQ-9, and GAD-7 ($P>0.05$) (Supplementary Table 3). In patients with CMD without diabetes mellitus, only age ($r=-0.335$, $P=0.012$) was negatively correlated with the MPRI. In CMD patients with diabetes mellitus, the MPRI did not correlate with the included risk factors ($P>0.05$).

Tables 3 and 4 show the logistic regression analysis of the MPRI and risk factors. Due to the synergistic effect of diabetes mellitus and HbA1c, they were included in the logistic regression analysis, respectively. Logistic regression analysis showed that HbA1c (OR = 2.336, 95% CI: 1.119–4.876, $P=0.024$) and diabetes mellitus (OR = 4.494, 95% CI: 1.225–16.485, $P=0.023$) were independent risk factors for MPRI reduction in patients with CMD. For those without diabetes mellitus, HbA1c was still predictive of a decline in MPRI (OR = 19.953, 95% CI: 1.743–93.449, $P=0.029$). However, in patients with diabetes mellitus, HbA1c could not predict a declined MPRI (OR = 0.984, 95% CI: 0.265–3.658, $P=0.981$).

Table 3
Logistic regression analysis (including HbA1c)

Factor	ALL		Without diabetes mellitus		With diabetes mellitus	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Gender(male)	2.032(0.411,10.035)	0.384	1.014(0.071,14.529)	0.992	0.448(0,6.462)	0.826
Age	1.020(0.929,1.119)	0.683	1.000(0.876,1.142)	0.999	1.105(0.884,1.381)	0.381
UA	0.992(0.981,1.003)	0.148	1.002(0.984,1.019)	0.863	0.984(0.957,1.011)	0.251
HCY	0.995(0.913,1.084)	0.902	0.985(0.865,1.121)	0.820	0.987(0.785,1.240)	0.910
PHQ-9	1.053(0.863,1.286)	0.611	1.081(0.817,1.431)	0.587	0.886(0.407,1.928)	0.886
GAD-7	1.030(0.849,1.248)	0.766	1.245(0.894,1.735)	0.195	1.259(0.597,2.654)	0.545
HbA1c	2.336(1.119,4.876)	0.024*	19.953(1.743,93.449)	0.029*	0.984(0.265,3.658)	0.981
UA, uric acid;HCY, Homocysteine; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder Questionnaire-7; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; *p < 0.05						

Table 4
Logistic regression analysis (including diabetes mellitus)

Factor	OR (95%CI)	P value
Gender(male)	1.316(0.328,5.285)	0.682
Age	1.013(0.948,1.082)	0.611
UA	0.993(0.984,1.002)	0.138
HCY	0.964(0.885,1.051)	0.403
PHQ-9	1.037(0.889,1.209)	0.646
GAD-7	0.996(0.846,1.172)	0.957
Diabetes mellitus	4.494(1.225,16.485)	0.023*
UA, uric acid;HCY, Homocysteine; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder Questionnaire-7; *p < 0.05		

Discussion

In this study, we demonstrated that HbA1c levels were negatively correlated with the MPRI, and that HbA1c was an independent risk factor for the decline in MPRI in patients with CMD, especially in those without diabetes mellitus.

CMD is a clinical syndrome of recurrent angina pectoris without obstructive epicardial arteries. At present, coronary microvascular dysfunction can lead to a decrease in the MPRI. The MPRI is a new prognostic index for patients with non-obstructive coronary heart disease¹⁶. Zhou et al. found that compared with patients with an MPRI of > 1.47, patients with an MPRI of ≤ 1.47 had a threefold increased risk of MACEs (hazard ratio[HR]:3.14;95% CI:1.58 ~ 6.25;p 0.001)¹⁶. Therefore, according to the classification index of an MPRI of ≤ 1.47 , patients with CMD were divided into two groups, and the risk factors of an MPRI decline were explored by comparing the clinical characteristics of patients with an MPRI of ≤ 1.47 and those with an MPRI of > 1.47.

Our study found that HbA1c in patients with an MPRI of ≤ 1.47 was significantly higher than that in the group with an MPRI of > 1.47 [6.30 (5.70, 7.70) vs. 5.80 (5.60, 6.50)]. HbA1c was negatively correlated with the MPRI ($r=-0.349$, $P = 0.001$), and HbA1c was an independent risk factor for a declined MPRI in patients with CMD (OR = 2.336, 95% CI: 1.119–4.876, $P = 0.024$), and CMD patients without diabetes mellitus (OR = 19.953, 95% CI: 1.743–93.449, $P = 0.029$). However, in patients with diabetes mellitus, HbA1c was not related to the MPRI ($r=-0.345$, $P = 0.107$) and was not an independent predictor of an MPRI decline (OR = 0.984, 95%CI:0.265–3.658). Our findings indicate that HbA1c can predict the MPRI in patients with prediabetes; however, for patients diagnosed with diabetes mellitus, blood sugar control (HbA1c) cannot affect the MPRI. This indicated that microvascular changes occurred in the early stages of diabetes mellitus, and the control of blood sugar cannot be reversed. Therefore, early detection and active prevention are the most effective treatments.

This result is similar to that of a previous study showing that diabetes is an independent risk factor for CMD and reduction of the MPRI¹⁵ when diabetes was brought into the logistic regression analysis independent of HbA1c. HbA1c is the gold indicator of blood glucose control, and HbA1c 6.0–6.5% is defined as a high-risk group for diabetes, and effective preventive measures should be implemented¹⁷. Moreover, studies have shown that cardiovascular pathological changes in diabetes have already occurred in the early stages of disease, and are progressively aggravated with the ongoing disease, which is similar to our result¹⁸.

Previous studies have shown a significant relationship between blood glucose control and cardiovascular disease, with HbA1c being a predictor of cardiovascular disease¹⁹. The ACCORD study showed that HbA1c trajectory was associated with cardiovascular outcomes in type 2 diabetes patients with high cardiovascular risk⁸. Moreover, the ADVANCE study showed that intensive blood glucose control (HbA1c of < 6.5%) was associated with a decrease in major microvascular events instead of major macrovascular events²⁰. The potential link between blood glucose control, cardiovascular incidence rate, and mortality can be partly explained by CMD.

HbA1c makes haemoglobin easy to glycosylate through long-term hyperglycaemia and easily forms advanced glycation end products (AGEs). The main mechanism is to induce the production of reactive oxygen species causing oxidative stress and inactivating nitric oxide, thereby reducing its bioavailability and causing damage to the endothelium-dependent relaxation function²¹. In contrast, AGEs may disrupt the balance of endothelial cells by reducing prostacyclin and increasing the expression of endothelin¹²². As the glycosylation of haemoglobin increases, its ability to carry oxygen and release oxygen decreases, causing ischemia, hypoxia, and damage to vascular endothelial cells, resulting in microcirculation dysfunction.

Therefore, risk prevention strategies for patients with type 2 diabetes and prediabetes should include treatments specifically for CMD. Active measures should be taken to screen for CMD and control blood sugar from prediabetes to avoid the occurrence of microvascular complications. In addition, as a non-invasive, safe, and efficient CMD detection method, stress perfusion CMR should be widely used in the early diagnosis of CMD.

Limitations

First, this was a single-centre retrospective study that did not include follow-up information and evaluation of patient prognosis. Second, the sample size of this study was limited, and a large sample multicentre prospective study is required to provide more sufficient evidence.

Conclusions

HbA1c was an independent risk factor for the decrease in the MPRI in patients with CMD, especially in those without diabetes mellitus, but not in those with diabetes mellitus. High levels of HbA1c may participate in the pathological process of the occurrence and development of CMD, resulting in a decrease in the MPRI.

List Of Abbreviations

Advanced glycation end products, AGEs; adenosine triphosphate, ATP; Canadian Cardiovascular Society, CCS; coronary computed tomography angiography, CCTA; creatine kinase isoenzyme MB, CK-MB; coronary microvascular disease, CMD; cardiac magnetic resonance, CMR; cardiac troponin I, cTnI; fasting blood glucose, FBG; Generalized Anxiety Disorder Questionnaire-7, GAD-7; glycated haemoglobin A1c, HbA1cI; homocysteine, HCY; high-density lipoprotein cholesterol, HDL-C; invasive coronary angiography, ICA; interquartile range, IQR; low-density lipoprotein cholesterol, LDL-C; left ventricular ejection fraction, LVEF; major adverse cardiovascular events, MACEs; myocardial perfusion reserve index, MPRI; odds ratio, OR; percutaneous coronary intervention, PCI; Patient Health Questionnaire-9, PHQ-9; Seattle Angina Quality of Life Score, SAQ; total cholesterol, TC; triacylglycerol, TG; uric acid, UA; white blood cells, WBC.

Declarations

Ethics approval and consent to participate

This study has been approved by the institutional medical ethical committee of Beijing Anzhen Hospital, China (approval NO. KS2019014). All participants gave written informed consent.

Consent for publication

Each participant consented to participating in this study and publishing the result.

Availability of data and materials

Data and materials are available upon request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by Capital Health Development Research Project (No. 2018-2-2063), coronary artery microvascular disease innovation foundation (NO. 2018-CCA-CMVD-01), National Natural Science Foundation of China (NO. 81971569 and NO. 81671650), Beijing Lab for Cardiovascular Precision Medicine (PXM2018_014226_000013), Beijing Municipal Science and Technology Project (Z161100000516139), and 2018 Beijing Excellent Talent Fund (NO. 2018000021469G241).

Authors' contributions

Jingwen Yong and Jinfan Tian contributed to the manuscript draft. Xiantao Song conceived the topic and revised the manuscript. XueYao Yang and Xin Zhao contributed to data collection. JiaXin Cao, HuiHui Kong and Yi He contributed to CMR analysis.

Acknowledgements

We thank all patients who participated in the study.

Findings

This work was supported by Capital Health Development Research Project (No. 2018-2-2063), National Natural Science Foundation of China (NO. 81971569, NO. 81670324 and NO. 81671650), coronary artery microvascular disease innovation foundation (NO. 2018-CCA-CMVD-01), Beijing Lab for Cardiovascular Precision Medicine (PXM2018_014226_000013), Beijing Municipal Science and Technology Project (Z161100000516139), and 2018 Beijing Excellent Talent Fund (NO. 2018000021469G241).

References

1. Kunadian V, Chieffo A, Camici P, Berry C, Escaned J, Maas A, Prescott E, Karam N, Appelman Y, Fraccaro C, Louise Buchanan G, Manzo-Silberman S, Al-Lamee R, Regar E, Lansky A, Abbott J, Badimon L, Duncker D, Mehran R, Capodanno D and Baumbach A. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary

- Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *European heart journal*. 2020;41:3504-3520.
2. Marinescu M, Löffler A, Ouellette M, Smith L, Kramer C and Bourque J. Coronary microvascular dysfunction, microvascular angina, and treatment strategies. *JACC Cardiovascular imaging*. 2015;8:210-20.
 3. Kissel C, Chen G, Southern D, Galbraith P and Anderson T. Impact of clinical presentation and presence of coronary sclerosis on long-term outcome of patients with non-obstructive coronary artery disease. *BMC cardiovascular disorders*. 2018;18:173.
 4. Brainin P, Frestad D and Prescott E. The prognostic value of coronary endothelial and microvascular dysfunction in subjects with normal or non-obstructive coronary artery disease: A systematic review and meta-analysis. *International journal of cardiology*. 2018;254:1-9.
 5. Mejía-Rentería H, van der Hoeven N, van de Hoef T, Heemelaar J, Ryan N, Lerman A, van Royen N and Escaned J. Targeting the dominant mechanism of coronary microvascular dysfunction with intracoronary physiology tests. *The international journal of cardiovascular imaging*. 2017;33:1041-1059.
 6. Mygind N, Pena A, Mide Michelsen M, Ali Qayyum A, Frestad D, Emil Christensen T, Ali Ghotbi A, Hasbak P, Kjaer A, Vejlstrup N, Gustafsson I, Riis Hansen P, Steen Hansen H, Prescott E and Kastrup J. Myocardial first pass perfusion assessed by cardiac magnetic resonance and coronary microvascular dysfunction in women with angina and no obstructive coronary artery disease. *Scandinavian journal of clinical and laboratory investigation*. 2019;79:238-246.
 7. Morton G, Chiribiri A, Ishida M, Hussain S, Schuster A, Indermuehle A, Perera D, Knuuti J, Baker S, Hedström E, Schleyer P, O'Doherty M, Barrington S and Nagel E. Quantification of absolute myocardial perfusion in patients with coronary artery disease: comparison between cardiovascular magnetic resonance and positron emission tomography. *Journal of the American College of Cardiology*. 2012;60:1546-55.
 8. Wang JS, Liu WJ and Lee CL. HbA1c trajectory and cardiovascular outcomes: an analysis of data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study. *Therapeutic Advances in Chronic Disease*. 2021;12:204062232110263.
 9. Group IDFGD. Global guideline for type 2 diabetes. *Diabetes research and clinical practice*. 2014;104:1-52.
 10. Chalmers J and Cooper ME. UKPDS and the legacy effect. *N Engl J Med*. 2008;359:1618-20.
 11. Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjörnsdóttir S, Wedel H, Clements M, Dahlqvist S and Lind M. Excess Mortality among Persons with Type 2 Diabetes. *N Engl J Med*. 2015;373:1720-32.
 12. Lind M, Imberg H, Coleman RL, Nerman O and Holman RR. Historical HbA(1c) Values May Explain the Type 2 Diabetes Legacy Effect: UKPDS 88. *Diabetes care*. 2021.
 13. Group UPDSU. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). . *Lancet (London, England)*. 1998;352:837-53.
 14. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancina G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompont S, de Galan BE, Joshi R and Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560-72.
 15. Huang R, Abdelmoneim S, Nholo L, Basu R, Basu A and Mulvagh S. Relationship between glycosylated hemoglobin A1c and coronary flow reserve in patients with Type 2 diabetes mellitus. *Expert review of cardiovascular therapy*. 2015;13:445-53.

16. Zhou W, Chun J, Yin L, Leung ST and Ng MY. Long-Term Prognosis of Patients With Coronary Microvascular Disease Using Stress Perfusion Cardiac Magnetic Resonance. *JACC Cardiovascular imaging*. 2020.
17. Committee IE. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes care*. 2009;32:1327-34.
18. Brown RE, Riddell MC, Macpherson AK, Canning KL and Kuk JL. All-cause and cardiovascular mortality risk in U.S. adults with and without type 2 diabetes: Influence of physical activity, pharmacological treatment and glycemic control. *Journal of Diabetes & Its Complications*. 2014;28:311-315.
19. Holman RR, Paul SK, Bethel MA, Matthews DR and Neil H. 10-year follow-up of intensive glucose control in type 2 diabetes. *New England Journal of Medicine*. 2008;359:1577.
20. Patel A, Macmahon S, Chalmers J, Neal B and Fassett R. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetesThe ADVANCE Collaborative GroupN Engl J Med20083582560257218539916. *New England Journal of Medicine*. 2008;358.
21. Kajikawa M, Maruhashi T, Hidaka T, Matsui S and Higashi Y. Effect of Saxagliptin on Endothelial Function in Patients with Type 2 Diabetes: A Prospective Multicenter Study. *Scientific reports*. 2019;9:10206.
22. Sho-Ichi Yamagishi TM. Smooth muscle cell pathophysiology and advanced glycation end products (AGEs). *Current Drug Targets*. 2010;11:875-81.

Figures

Figure 1

Flow chart. CMR, Cardiac Magnetic Resonance; CMD, coronary microvascular disease; MPRI, myocardial perfusion reserve index.

Figure 2

MPRI derivation process. (A) Rest and stress imaging contouring. (B) Rest and stress SI curve. (C) Polar map demonstrates MPRI values in each segment. MPRI, myocardial perfusion reserve; SI, signal intensity.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [renamed53219.docx](#)