VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2024, Vol. 31, No. 2, 185–192
DOI: 10.5603/CJ.a2022.0100

ISSN 1897–5593
eISSN 1898–018X

Impaired coronary flow reserve in patients with poor type 2 diabetes control: Preliminary results from prospective microvascular dysfunction registry

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Abstract

Background: *Type 2 diabetes (DM) is a common comorbidity associated with cardiovascular disease, especially when poor glucose control is present. Extracardiac microcirculatory complications prevalence is well documented, however coronary microcirculatory dysfunction (CMD) seem to be underreported in this group.*

Methods: *The present study analyzed coronary physiology measurements (coronary flow reserve [CFR], index of microcirculatory resistance [IMR], resistance reserve ratio [RRR]) in 47 diabetic patients (21 subjects with poor glycemia control defined as fasting glucose levels > 7.2 mmol/L and 26 with normal fasting glucose), and compared to 54 non-diabetic controls, who had undergone coronary angiography due to symptoms of chronic coronary syndrome. The median age of patients was 65.5 [59.0; 73.0] years old, 74% male, similar in terms of cardiovascular risk factors and prior myocardial infarction. Insulin was used by 19% of diabetic patients with poor glucose control and by 15% of those with DM and low fasting glucose.*

Results: *Prevalence of CMD was 38% in poor glycemia control patients, 27% in DM-patients with proper glucose control and 31% of non-diabetics. Median CFR values were the lowest in poor DM control patients compared to both, normal fasting glucose (1.75 [1.37; 2.32] vs. 2.30 [1.75; 2.85], $p = 0.026$) and to non-diabetics (1.75 [1.37; 2.32] vs. 2.15 [1.50; 2.95], $p = 0.045$). Levels of IMR, RRR and microvascular resistance reserve did not differ significantly between compared groups ($p > 0.05$ for all comparisons).*

Conclusions: *Poor glycemia control in type 2 DM might be associated with a higher prevalence of CMD driven by decreased coronary flow reserve, however, further research in larger groups of patients should be performed to confirm this observation.* (Cardiol J 2024; 31, 2: 185–192)

Keywords: coronary artery disease, coronary microcirculatory dysfunction, diabetes mellitus, coronary flow reserve, index of microcirculatory resistance

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Received: 18.05.2022 Accepted: 18.08.2022 Early publication date: 27.10.2022

Introduction

Type 2 diabetes mellitus (DM) is a common comorbidity in the general population with a prevalence increasing worldwide, frequently diagnosed in patients with cardiovascular disease [1]. It leads to a wide range of vascular and non-vascular complications especially when associated with poor glucose control [1, 2]. Despite the improvement in medical treatment, diabetic patients still have an increased risk for microvascular and macrovascular complications compared to non-diabetic subjects [3]. Moreover, it has been recognized that coronary microvascular dysfunction (CMD) is an early condition in DM that may precede macrovascular disease leading to an accelerated development of obstructive coronary artery disease (CAD) [4]. Coronary flow reserve (CFR) is an index of microvascular function in patients without significant epicardial coronary artery stenosis and has been used to disclose impaired microcirculation by the means of bolus thermodilution [5]. The index of microcirculatory resistance (IMR) has been proposed as a simple, specific and reproducible invasive method of assessing coronary microcirculation, also relying on thermodilution [6]. IMR provides a measurement of the minimum achievable microcirculatory resistance in a target coronary artery territory, enabling a quantitative assessment of the microvascular integrity. Nevertheless, the presence and related pathological mechanisms underlying CMD in diabetic patients with poor DM control are still under-reported, following the limited ability to reliably assess coronary microcirculation. Therefore, the aim herein, was to assess the impact of higher fasting glucose levels on prevalence of CMD in patients with type 2 DM.

Methods

In this prospective cohort study, patients with symptoms of chronic coronary syndromes aged > 18 years with at least one borderline (i.e. > 40% and < 90% diameter stenosis) coronary lesion were included. Patients with significant CAD, acute coronary syndromes, decompensated heart failure, severe valvular disease, hypertrophic cardiomyopathy, chronic inflammatory disease, rheumatic disease, and an active neoplasm were excluded. The study protocol conformed with the ethical guidelines of the 1975 Declaration of Helsinki with later amendments. All patients gave informed consent. The study was approved by the institutional ethical board (application number 122.6120.262.2015, 19 Nov 2015).

Glucose metabolism assessment/optimal glycemiacontrol in diabetes

A fasting glucose level of 7.2 mmol/L was used to differentiate between patients with optimal diabetes control (Group B) and poor glycemiacontrol (Group C), as this value is needed to achieve HbA1c glucose levels < 7.0% [7]. HbA1c levels itself were measured by the High Performance Liquid Chromatography (HPLC) method, however, the methodology was changed during study recruitment and therefore it was not used to differentiate between good and poor glycemiacontrol. Non-diabetic patients were qualified as the control (Group A).

Invasive coronary angiography and physiological measurements

Invasive coronary angiography was recorded with standard perpendicular projections, using a 6 French diagnostic catheter. Quantitative coronary angiography (QCA) was performed by an independent core lab analyst blinded to the results of coronary physiology, with the use of the edge detection system (CAAS 5.7 QCA system, Pie Medical).

Resting full-cycle ratio (RFR)

The RFR was calculated as the lowest filtered Pd/Pa (a mean distal coronary pressure [Pd] to aortic pressure [Pa]) value from four consecutive cardiac cycles, using Coroflow software ver. 3.0 (Abbott, US). A value of 0.89 was set as a cut-off for significant epicardial stenosis [8].

Fractional flow reserve (FFR)

Fractional flow reserve was calculated as a mean distal coronary pressure (Pd) to aortic pressure (Pa) ratio during stable hyperemia achieved with a continuous intravenous infusion of 140 μg/ /kg/min of adenosine, using a Pressure Wire X sensor (Abbott, US) and Coroflow software ver. 3.0 (Abbott, US) [9, 10].

Coronary flow reserve (CFR)

Thermodilution-based CFR was assessed using Pressure Wire X (Abbott, US) with the achievement of full hyperemia with continuous intravenous infusion of 140 μg/kg/min of adenosine [11]. An abnormal value of CFR < 2.0 was assumed and was attributed to coronary microcirculatory dysfunction when no significant epicardial stenosis was present [12].

Index of microcirculatory resistance (IMR)

Hyperemic mean time of saline transit and distal coronary pressures during full hyperemia were used for the IMR calculation [6]. FFR values obtained during hyperemia were used to calculate corrected IMR, according to Yongs' formula [13]. The cut-off value for abnormal IMR was ≥ 25.

Resistive reserve ratio (RRR)

A resistive reserve ratio was calculated using IMR, baseline mean transit time and distal coronary pressure to assess vasodilatory microcirculation capacity [14].

Microvascular resistance reserve (MRR)

Coronary flow reserve, baseline aortic pressures and hyperemic coronary distal pressures were used to calculate MRR (Equation 1), as proposed by De Bruyne et al. [15, 16].

$$MRR = CFR \times \frac{P_{aortic\ at\ rest}}{P_{distal\ at\ hyperemia}} \quad \text{(Equation 1)}$$

Coronary microcirculatory dysfunction

Patient was diagnosed with CMD when abnormal values of IMR (≥ 25) or CFR < 2.0 (in case of no significant stenosis) were recorded in any of tested vessels [12].

Statistical analysis

Normality of values distribution was assessed with the Shapiro-Wilk test. Continuous values were presented as a mean with standard deviation for normal distribution and otherwise as a median with interquartile range. Comparisons between multiple groups were performed using ANOVA F-test and the Kruskal-Wallis test, respectively. Categorical variables were presented as proportions of groups and compared using χ^2 test. A criterion of $\alpha \leq 0.05$ for two-sided test was considered significant. Calculations were performed using R language version 4.0 (R Foundation for Statistical Computing, Vienna, Austria), with Tidyverse package ecosystem for computation and ggplot2 package for visualization.

Results

Patient level analysis

Group characteristics. In this prospective observational study 101 patients, 54 non-diabetic (Group A), 26 with well controlled diabetes (Group B) and 21 with poor controlled diabetes (Group C) were included. Median age of patients was 65 years and was similar in all groups. About 25% of analyzed patients were female. All groups were similar in terms of body mass index (BMI), history of arterial hypertension, dyslipidemia, or prior myocardial infarction (MI). Left ventricular ejection fraction (LVEF) was similar in all groups, however poor controlled DM patients had higher left ventricular mass index compared to non-diabetics (128 vs. 96 g/m^2, p = 0.004 for post hoc analysis). All patients were diagnosed with chronic coronary syndromes, without any significant differences in terms of angina according to Canadian Cardiovascular Society (CCS) class on admission. All groups were also similar in terms of antiplatelet therapy, statin use, beta-blockers or antihypertensive drugs. Detailed patient characteristics are presented in Table 1.

Diabetes treatment and glycemia control. Over 60% of all diabetic patients used metformin without significant differences between groups B and C. Patients with poor controlled DM were treated with insulin more often than well controlled diabetic patients (20% vs. 15%, p = 0.02 for χ^2 test). Neither of these groups of patients used SGLT2 inhibitors nor GLP-1 inhibitors. Patients with poor controlled DM had significantly higher levels of fasting glucose compared to non-diabetics and well controlled DM (median 9.9 [8.1; 11.0] mmol/L vs. 5.4 [5.1; 6.0] mmol/L, p < 0.001 and 9.9 mmol/L vs. 5.8 [5.3; 6.7] mmol/L, p < 0.001 in *post hoc* analysis, respectively). Similarly, HbA1c levels were significantly higher in patients with poor controlled DM as compared to both, well controlled DM and non-diabetics (7.7 [6.6; 7.9]% vs. 6.1 [5.6; 6.7]%, p = 0.004 and 7.7 [6.6;7.9]% vs. 5.7 [5.3; 5.9]% mmol/L, p < 0.001, respectively). In all cases diabetes was diagnosed prior to the index hospitalization. A detailed comparison of groups is presented in Table 1.

CMD diagnosis. Microcirculatory dysfunction prevalence was the highest in group C (38% of patients with poor glycemic control), however the difference between groups was not statistically significant. Details are presented in Figure 1.

Per vessel analysis

Alongside with patient level analysis, per vessel analysis was performed. Detailed results are presented in Table 2.

Coronary angiography. A total of 157 coronary arteries were analyzed, predominantly (over 57%) left anterior descending (LAD). Median diameter stenosis was 45% with interquartile range (IQR) from 40% to 50%. RFR values were similar in all compared groups, with median of 0.89 (p = 0.877).

Table 1. Baseline patient characteristics, pharmacotherapy, and laboratory results.

	Total (n = 101)	Group A (Non-diabetic; n = 54)	Group B (Well controlled DM; n = 26)	Group C (Poor controlled DM; n = 21)	P value
Demography and medical history					
Age [years]	65.5 [59.0;73.0]	64.5 [59.0;69.8]	68.0 [63.0;74.0]	66.0 [59.0;73.0]	0.274
Female sex	26 (25.7%)	14 (25.9%)	9 (34.6%)	3 (14.3%)	0.285
BMI [kg/m^2]	28.1 [26.0;31.8]	27.9 [25.0;31.2]	29.1 [27.7;30.9]	29.6 [26.0;35.3]	0.091
Dyslipidemia or statin use	92 (91.1%)	47 (87.0%)	24 (92.3%)	21 (100%)	0.257
Arterial hypertension	97 (96.0%)	52 (94.5%)	25 (96.2%)	20 (100%)	0.811
Prior AMI	25 (27.8%)	11 (23.9%)	10 (41.7%)	4 (20.0%)	0.197
Smoking status:					0.192
Never	52 (55.9%)	26 (53.1%)	17 (70.8%)	9 (45.0%)	
Current or former	41 (44.1%)	23 (46.9%)	7 (29.2%)	11 (55.0%)	
Angina according to CCS scale:					0.656
0	21 (20.8%)	9 (16.7%)	6 (23.1%)	6 (28.6%)	
1	30 (29.7%)	17 (31.5%)	8 (30.8%)	5 (23.8%)	
2	36 (35.6%)	20 (37.0%)	7 (26.9%)	9 (42.9%)	
3	14 (13.9%)	8 (14.8%)	5 (19.2%)	1 (4.76%)	
Dyspnea according to NYHA class:					0.891
0	56 (55.4%)	32 (59.3%)	13 (50.0%)	11 (52.4%)	
1	12 (11.9%)	6 (11.1%)	4 (15.4%)	2 (9.52%)	
2	30 (29.7%)	14 (25.9%)	9 (34.6%)	7 (33.3%)	
3	3 (2.97%)	2 (3.70%)	0 (0.00%)	1 (4.76%)	
Laboratory results					
Hemoglobin [g/dL]	13.8 [12.9;15.0]	14.0 [13.4;14.9]	13.4 [12.1;14.3]	14.0 [12.7;15.6]	0.096
LDL [mmol/L]	2.22 [1.79;2.86]	2.24 [1.92;2.80]	2.05 [1.64;2.26]	2.51 [2.14;3.45]	0.069
TG [mmol/L]	1.29 [0.93;1.82]	1.29 [0.90;1.81]	1.20 [0.94;1.64]	1.52 [1.03;1.92]	0.451
eGFR CKD	78.0 [65.0;90.0]	80.0 [72.0;90.5]	73.5 [60.5;83.2]	86.0 [57.0;93.0]	0.110
Fasting glucose [mmol/L]	5.80 [5.30;7.20]	5.40 [5.10;6.00]	5.80 [5.32;6.68]	9.90$^{\#}$ [8.10;11.0]	**< 0.001**
HbA1c [%]	5.80 [5.50;6.50]	5.70 [5.30;5.90]	6.05$^{\#\#}$ [5.57;6.67]	7.70$^{\#}$ [6.55;7.90]	**< 0.001**
CMD final diagnosis					0.381
CMD	32 (31.7%)	17 (31.5%)	7 (26.9%)	8 (38.1%)	
Non-CMD	19 (18.8%)	7 (13.0%)	8 (30.8%)	4 (19.0%)	
Revascularization	50 (49.5%)	30 (55.6%)	11 (42.3%)	9 (42.9%)	
Echocardiography					
LVEF [%]	55.0 [50.0;60.0]	58.5 [50.0;60.0]	56.0 [50.5;60.0]	50.0 [40.0;60.0]	0.054
LVMI [g/m^2]	106 [88.9;128]	95.7 [86.8;115]	108 [83.0;130]	128 [108;139]$^{\#}$	**0.006**
Coronary artery disease:					0.190
Single vessel	51 (51.0%)	26 (48.1%)	18 (69.2%)	7 (35.0%)	
Dual vessel	38 (38.0%)	21 (38.9%)	7 (26.9%)	10 (50.0%)	
Triple vessel	11 (11.0%)	7 (13.0%)	1 (3.85%)	3 (15.0%)	
Gensini score	9.50 [6.00;14.0]	10.0 [7.00;15.6]	7.25 [5.00;11.0]	9.50 [5.00;11.5]	0.255
SBP [mmHg]	136 [122;151]	131 [120;151]	136 [120;150]	146 [134;156]	0.339
Pharmacotherapy					
Metformin	29 (28.7%)	NA	16 (61.5%)$^{\#\#}$	13 (65.0%)$^{\#}$	< 0.001
Insulin	8 (7.92%)	NA	4 (15.4%)	4 (20.0%)	0.002
ASA	91 (90.1%)	49 (90.7%)	21 (80.8%)	21 (100%)	0.095
ACEI/ARB	91 (91.0%)	49 (90.7%)	25 (96.2%)	17 (85.0%)	0.462
Statin use	99 (98.0%)	53 (98.1%)	26 (100%)	20 (95.2%)	0.439
Beta-blockers	86 (85.1%)	44 (81.5%)	23 (88.5%)	19 (90.5%)	0.604
Non-dihydropyridines CCA	9 (9.00%)	3 (5.56%)	2 (8.00%)	4 (19.0%)	0.205
Dihydropyridines CCA	33 (32.7%)	17 (31.5%)	10 (38.5%)	6 (28.6%)	0.744

Data are shown as number (%) or mean [interquartile range]; ACEI/ARB — angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AMI — acute myocardial infarction; BMI — body mass index; CCA — calcium channel antagonist; CMD — coronary microcirculatory dysfunction; eGFR-CKD — estimated glomerular filtration rate using CKD-EPI formula; LDL — low density lipoprotein; LVEF — left ventricle ejection fraction; LVMI — left ventricle mass index; NA — not applicable; NYHA — New York Heart Association; SBP — systolic blood pressure; TG — triglycerides; $^{\#}p < 0.05$ Group C vs. A; $^{\#\#}p < 0.05$ Group B vs. A

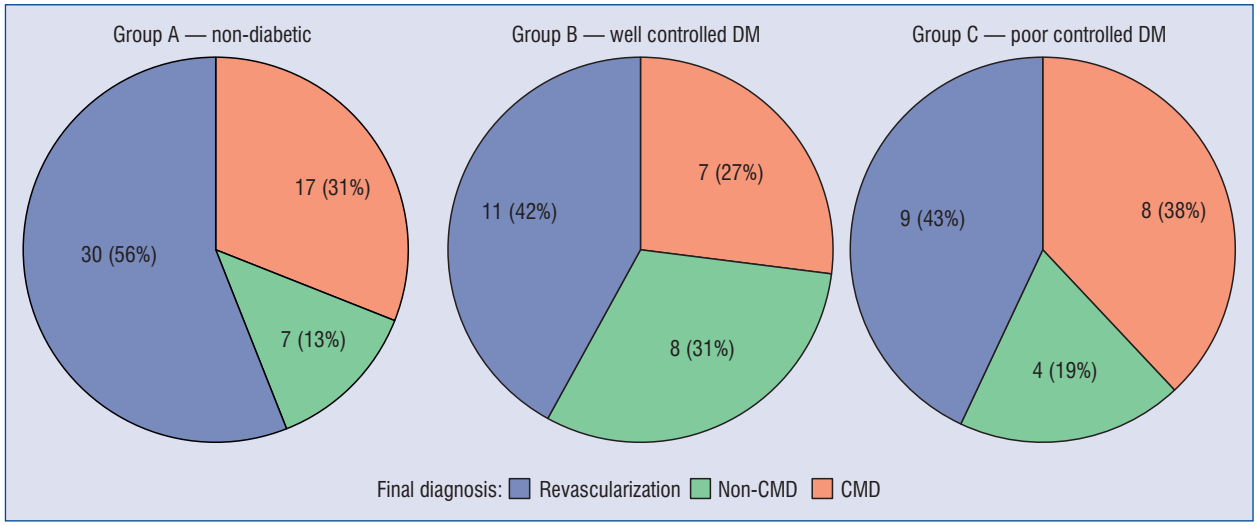

Figure 1. Coronary microcirculatory dysfunction prevalence according to diabetes mellitus (DM) status. Patients without diabetes (Group A), well controlled DM (Group B) and poor controlled DM (Group C); CMD — coronary microvascular dysfunction; p = 0.37.

Table 2. Per vessel analysis of coronary angiography and coronary physiology measurements.

	Total (n = 157)	Group A (Non-diabetic; n = 90)	Group B (Well controlled DM; n = 31)	Group C (Poor controlled DM; n = 36)	P value
Vessel diagnosed					0.270
LAD	88 (57.1%)	48 (54.5%)	20 (64.5%)	20 (57.1%)	
LCx	39 (25.3%)	20 (22.7%)	7 (22.6%)	12 (34.3%)	
RCA	27 (17.5%)	20 (22.7%)	4 (12.9%)	3 (8.57%)	
QCA					
Diameter stenosis	45.0 [40.0;50.0]	45.0 [40.0;50.0]	46.0 [39.0;48.0]	45.5 [40.5;48.5]	0.917
Reference diameter	2.67 [2.38;2.97]	2.67 [2.48;2.97]	2.78 [2.54;3.04]	2.51 [2.29;2.93]	0.314
Physiologic measurements					
RFR	0.89 [0.84;0.94]	0.90 [0.85;0.94]	0.89 [0.83;0.93]	0.89 [0.84;0.94]	0.877
FFR	0.84 [0.78;0.91]	0.83 [0.76;0.90]	0.84 [0.78;0.90]	0.84 [0.80;0.91]	0.640
FFR ≤ 0.80	51 (32.5%)	31 (35.5%)	11 (29.0%)	9 (25.7%)	0.636
CFR	2.10 [1.50;2.70]	2.15 [1.50;2.95]	2.30 [1.75;2.85]	1.75 [1.37;2.32] $^{\#,\#\#}$	0.020
RRR	2.70 [1.80;3.70]	2.60 [1.90;3.90]	3.00 [2.10;3.85]	2.65 [1.60;3.30]	0.100
MRR	2.85 [1.98;3.89]	2.71 [1.97;3.97]	3.19 [2.11;4.16]	3.05 [1.74;3.31]	0.573
IMR	19.8 [13.1;28.5]	21.1 [12.8;30.1]	21.9 [15.3;27.9]	15.2 [12.7;21.9]	0.095

Data are shown as number (%) or mean [interquartile range]; CFR — coronary flow reserve; FFR — fractional flow reserve; IMR — index of myocardial resistance; LAD — left anterior descending artery; LCx — left circumflex branch; QCA — quantitative coronary angiography; RCA — right coronary artery; RFR — resting full cycle ratio; RRR — relative resistive ratio; $^{\#}$p < 0.05 Group C vs. B; $^{\#\#}$p < 0.05 Group C vs. A

Median FFR value was 0.84 and did not differ between groups. In 51 cases (32% of vessels), lesions were hemodynamically significant (i.e., FFR ≤ 0.80), and were qualified for revascularization.

CFR, IMR, RRR and MRR measurements results. CFR values were significantly lower in patients with poor controlled DM as compared to both, non-diabetic and well controlled DM group

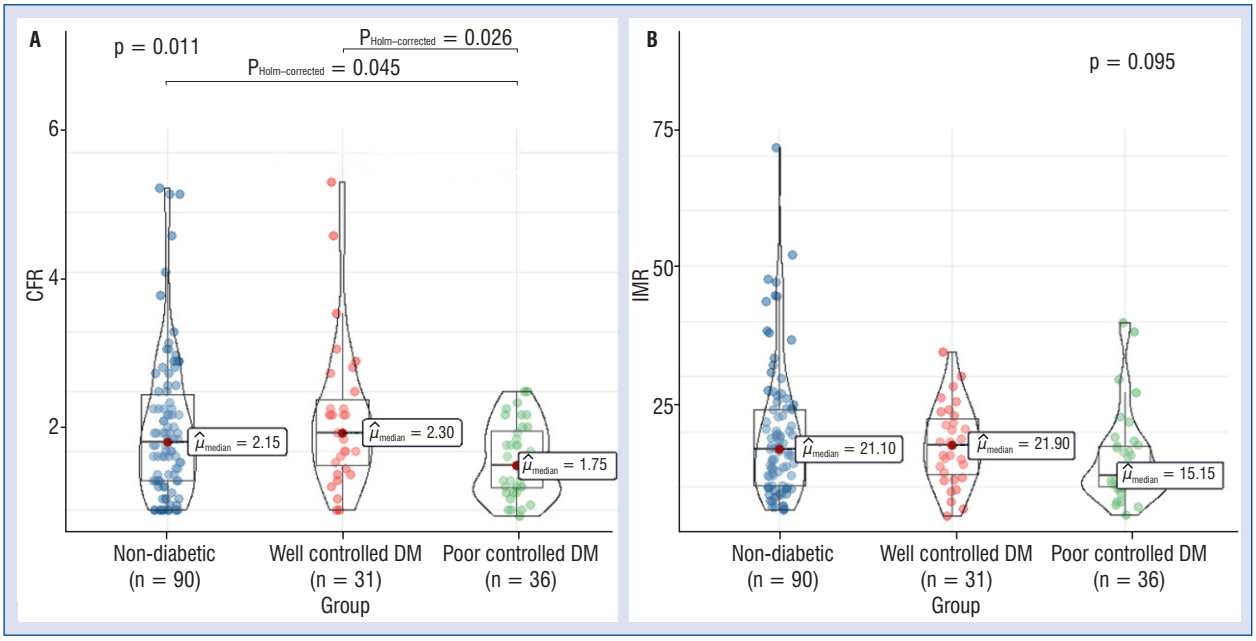

Figure 2. Microcirculatory indices comparison; **A.** Coronary flow reserve (CFR) values according to diabetes status; **B.** Index of Microcirculatory Resistance (IMR) levels according to diabetes status; DM — diabetes mellitus.

(1.75 vs. 2.3, p = 0.026, 1.75 vs. 2.15, p = 0.026, respectively, overall p = 0.02). RRR was the highest in patients with well controlled DM, however the difference was not statistically significant. Similarly, no significant difference in IMR and MRR values between analyzed groups were observed. Detailed results are presented in Table 2 and Figure 2.

Discussion

The present study aimed to compare CMD prevalence in type 2 DM patients with well controlled diabetes and subjects with poor DM control. The main findings of this study are following: (1) in patients with poor controlled diabetes there are lower CFR values as compared to both with non-diabetic patients and patients with good fasting glucose levels; (2) level of coronary microcirculatory dysfunction may be associated with fasting glucose levels.

Microcirculatory dysfunction usually precedes structural myocardial changes; thus, the evolving ability to an early assessment of CMD holds great potential for risk stratification and patient therapy. In the current study, CMD prevalence measured by thermodilution derived indices was highest in the poor glucose control group and was present in 38% of patients. No similar data was found using CMD definition from current European Society of Cardiology (ESC) guidelines on chronic coronary syndromes and based on thermodilution assessment [12]. Noninvasive studies, as reported by Osborne et al. [17] suggest even higher prevalence of CMD to be present in over 59% diabetic patients diagnosed with positron emission tomography (PET) myocardial perfusion imaging. Similarly, Murthy et al. [3] observed impaired CFR in over 51% of diabetic patients in PET imaging.

In diabetic patients several risk factors of CMD were reported, including presence of arterial hypertension, dyslipidemia or higher BMI levels [5]. In the present analysis there were no significant differences between groups in terms of arterial hypertension nor presence of dyslipidemia, moreover almost all patients in our cohort were treated for these reasons. On the other hand, numerically higher median value of BMI was observed in group with poor glycemic control, without achieving a statistically significant level.

CFR values in diabetes

Increased prevalence of CMD in DM patients might be driven by decreased CFR values, increased IMR or both. In the present cohort CFR values were significantly lower in poor glucose control group and IMR levels were similar between all three groups. In recently published study by Gallinoro et al. [16], patients without significant coronary stenosis and DM type 2 had lower CFR values, mean 2.38, compared to non-diabetic

patients, however this analysis consisted of only 21 DM patients and authors did not elaborate on dependence of CFR on glucose levels [16]. Similar observation were made by Leung et al. [18], who reported CFR value of 2.76 in anterior coronary circulation and 4.35 in posterior coronary circulation in 32 diabetic patients, both significantly lower than measured in non-diabetic patients. The current analysis included a higher number; 47 patients with DM type 2, and results suggested that lower CFR values might be associated with poor glycemia control.

In exploratory analysis, CFR values were used as a surrogate to calculate novel index proposed recently by De Bruyne et al. [15], and found no significant difference between MRR values in analyzed groups, even though MRR was numerically higher in both diabetic groups when compared to the non-diabetic control.

CFR values according to glucose levels

Large epidemiological studies have shown a link between glucose levels and diabetic microvascular complications [19–21]. Moreover, intensive diabetes therapy leading to lower HbA1c levels has been proven to influence course of cardiovascular complications in DM patients [22]. Mechanism in which CFR is impaired by poor glycemia control remains unclear. Glucose level variability amplitude has been recently reported to correlate with CFR values, regardless of DM presence [23]. Furthermore, impaired coronary flow velocity ratio was associated with significantly higher fasting glucose concentration in diabetic women. Noteworthy, the difference was not observed in men [24]. In the present analysis, CFR values were significantly lower in poor controlled diabetes compared to both non-diabetics and patients with diabetes and fasting glucose < 7.2 mmol/L. This result is consistent with published data, however further research in larger populations is needed to confirm the above mentioned observation.

Limitations of the study

The present study results should be interpreted considering some limitations. This study is a preliminary report of results obtained from a relatively small group of patients, which might influence the significance level of comparisons, on the other hand a group of 47 diabetic patients seems to be one of the biggest cohorts who have been diagnosed with thermodilution based on invasive indices to date. Unfortunately, data on diabetes duration was not available in patient medical records.

Secondly, the glycemia control in patients was assessed by fasting glucose serum concentration, not by the HbA1c levels, as at the time of study recruitment HPLC methodology was still evolving, with no single standard. On the other hand, 7.2 mmol/L cut off value is a good predictor of obtaining HbA1c levels < 7.0%, which is the current goal of treatment according to ESC guidelines [1].

Thirdly, coronary microcirculatory dysfunction was diagnosed using indirect thermodilution based methodology, however IMR and CFR measurements are among methods proposed by contemporary chronic coronary syndromes ESC guidelines [25]. Taking into consideration above, results of presented study are rather hypothesis generating, and requires further research.

Conclusions

It was found that in patients with poor controlled diabetes there are lower CFR values as compared both with non-diabetic patients and patients with good fasting glucose levels. Moreover, level of coronary microcirculatory dysfunction may be associated with fasting glucose levels.

Acknowledgments

The present research was funded from statutory grant from the Department of Interventional Cardiology, Jagiellonian University Medical College [No. K/DSC/003585].

Conflict of interest: None declared

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