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Invasive coronary physiology assessment and predictors of coronary microvascular dysfunction in patients with diabetes mellitus☆

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ABSTRACT

Background: Diabetes mellitus (DM) has been associated with coronary microvascular dysfunction (CMD) in previous non-invasive studies. However, invasive studies have shown conflicting results.
Methods: To evaluate the prevalence and predictors of CMD in diabetic patients, invasive coronary physiology data of patients with fractional flow reserve (FFR) > 0.80 on the target vessel were analyzed from the BELmicro registry. Coronary flow reserve (CFR) < 2.5 and index of microcirculatory resistance (IMR) ≥ 25 were considered abnormal.
Results: Out of 402 patients, 72 had DM. Diabetic patients were older [69(61, 75) vs 64(58, 73), p = 0.02] and had higher rates of hypertension (73 % vs 56 %, p = 0.009) and dyslipidemia (89 % vs 64 %, p < 0.001) compared to non-diabetics. No differences were found between diabetic and non-diabetic patients in FFR [0.92 (0.89, 0.94) vs 0.91(0.88, 0.94), p = 0.8] and CFR [3.0(2.1, 4.4) vs 2.8(2.0, 4.1), p = 0.4]. IMR was slightly lower in diabetics [16(9, 24) vs 18(12, 27), p = 0.04], but the rate of abnormal IMR was comparable to non-diabetics (23 % vs 31 %, p = 0.2). Prevalence of CMD was similar between diabetics and non-diabetics (46 % vs 48 %, p = 0.8). Rates of CMD were comparable between patients with longstanding DM (≥10 years) and recent diagnosis (52 % vs 35 %, p = 0.2). No association was found between glycated hemoglobin levels and CFR and IMR. Female sex was the only independent predictor of CMD in diabetics (OR: 2.71, 95 % CI: 1.02, 7.50, p = 0.049).

Abbreviations: CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; DM, diabetes mellitus; FFR, fractional flow reserve; HbA1c, glycated hemoglobin; IMR, index of microcirculatory resistance; LVEF, left ventricular ejection fraction; Tmn, mean transit time; Pa, mean aortic pressure; Pd, mean distal pressure; RRR, resistive reserve ratio.

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Conclusions: No differences in prevalence of CMD were found between diabetic and non-diabetic patients. Longstanding diabetes, glycemic control and concomitant cardiovascular risk factors were not associated with CMD in diabetic patients.

1. Introduction

Diabetes mellitus (DM) is associated with an increased risk of macro- and microvascular complications as prolonged hyperglycemia enhances oxidative stress, which is responsible for endothelial dysfunction and vascular damage (Ahmad et al., 2022; Paneni et al., 2013). For this reason, diabetic patients have an increased risk of coronary artery disease (CAD) and cardiovascular mortality (Haffner et al., 1998; Roffi et al., 2011; Radke and Schunkert, 2010). In addition, the pathophysiological mechanisms of DM may affect coronary microvascular function (Yokoyama et al., 1997; Pitkänen et al., 1998) and determine worse clinical outcomes (Gdowski et al., 2020; Kelshiker et al., 2022).

Coronary physiology assessment allows diagnosis and risk stratification of patients with suspected coronary microvascular dysfunction (CMD) (Ford et al., 2020a; Benedetti et al., 2023; Maurina et al., 2023). Moreover, microvascular function evaluation leads to a tailored therapeutic approach, which has been shown to improve patients' symptoms and quality of life (Ford et al., 2018; Ford et al., 2020b). Bolus thermodilution is the most commonly used invasive technique to investigate coronary physiology (Barbato, 2004). It is based on the assumption that coronary blood flow is inversely related to the transit time of blood in the coronary artery and provides measurements of coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) (De Bruyne et al., 2001; Fearon and Kobayashi, 2017). Recently, two distinct CMD endotypes have been described in the literature: 1) functional CMD, characterized by abnormal CFR and normal IMR due to increased coronary flow at rest; 2) structural CMD, determined by both abnormal CFR and IMR due to reduced hyperemic coronary flow (Rahman et al., 2020).

Several previous studies, using different non-invasive diagnostic techniques, have attempted to assess the prevalence of CMD in diabetic patients, and some have confirmed of microvascular disease (Yokoyama et al., 1997; Pitkänen et al., 1998; Sezer et al., 2016; Atar et al., 2012). On the other hand, few studies have assessed coronary microvascular function using invasive techniques, and these have shown conflicting results (Gallinoro et al., 2021; Hwang et al., 2021; Leung and Leung, 2016; Picchi et al., 2011; Melikian et al., 2007; Chitturi et al., 2025). Furthermore, the distribution of CMD endotypes in diabetics has never been described. The current subanalysis of the BELmicro registry aimed to evaluate the prevalence of CMD and its endotypes in diabetic patients and to assess potential predictors of CMD.

2. Methods

2.1. Study population

The study population was derived from the Belgian national registry on coronary function testing (BELmicro registry, NCT06089031). Specifically, the BELmicro study is a prospective, observational, multicenter registry conducted in 14 centers in Belgium, which included all patients who underwent clinically indicated coronary function testing and could provide written informed consent (Bringmans et al., 2024). For the current analysis, patients who underwent coronary physiology assessment with bolus thermodilution and had a fractional flow reserve (FFR) >0.80 were selected, in order to exclude the presence of obstructive coronary artery disease in the target vessel. The condition of DM was defined in the presence of a reported history of DM or fasting plasma glucose $\geq$126 mg/dL or glycated hemoglobin (HbA1c) $\geq$6.5 % (or $\geq$48 mmol/mol). Longstanding diabetes was defined as having DM diagnosed for $\geq$10 years. All patients signed a written informed consent. The study protocol was in accordance with the Declaration of Helsinki. The central ethics committee of Antwerp University Hospital (Project ID 2021-0522) and the ethics committees of the participating centers approved the study protocol.

2.2. Aims of the study

The aims of the current subanalysis of the BELmicro registry were to evaluate the prevalence of CMD and its endotypes in diabetic patients, to compare the prevalence of CMD in patients with longstanding diabetes versus those with a more recent diagnosis, and to explore potential predictors of CMD in diabetic patients.

2.3. Invasive coronary physiology assessment

Coronary physiology assessment was performed with the bolus thermodilution method, using a pressure-temperature sensor tipped guidewire (Pressure Wire X, Abbott Vascular, Santa Clara, CA). The study protocol for the invasive assessment of coronary physiology has been described previously (Bringmans et al., 2024). Briefly, the pressure sensor of the guidewire was equalized at the tip of the guiding catheter and intracoronary nitrate (100 or 200 μg) was administered before the procedure. Room-temperature saline was injected in the coronary artery for three times at rest and during hyperemia to obtain the resting mean transit time (Tmn) and hyperemic Tmn, respectively. The mean distal pressure (Pd) and the mean aortic pressure (Pa) were recorded during the procedure. In case of pressure drift >0.02 at the end of the FFR pullback, the guidewire was re-equalized and pressure-derived indices were repeated. Intravenous infusion of adenosine (140 μg/kg/min) or intracoronary bolus injection of papaverine (12–16 mg) were administered to induce hyperemia. All physiology measurements were calculated and recorded in a dedicated software (Coroflow®, Coroventis, Uppsala, Sweden).

2.4. Coronary physiology indices and CMD endotypes

FFR was obtained as the lowest average of 3 consecutive beats of the ratio between hyperemic Pd and Pa (Pijls et al., 1996). CFR was determined as the ratio between resting and hyperemic Tmn (De Bruyne et al., 2001). IMR was calculated by multiplying the hyperemic Tmn and Pd during hyperemia (Fearon et al., 2003). CFR values <2.5 and IMR values $\geq$25 were considered abnormal (Fearon et al., 2003; Demir et al., 2022). The resistive reserve ratio (RRR) was obtained by dividing the product of the resting Tmn and resting Pd to the IMR (Lee et al., 2020). The diagnosis of CMD was defined by abnormal CFR and/or abnormal IMR. Functional CMD was determined by abnormal CFR and normal IMR, while structural CMD by both abnormal CFR and IMR.

2.5. Statistical analysis

Continuous variables with normal distribution are reported as mean $\pm$ standard deviation (SD). Continuous variables without normal distribution are reported as median and interquartile range (IQR). Normality in the distribution was verified by the Shapiro-Wilk test. Mean values were compared with Student *t*-test and median values were compared with Wilcoxon rank test. Categorical variables are reported as counts and percentages and were compared by the Pearson's Chi-square test and the Fisher's exact test as appropriate. Linear regression analysis was performed to evaluate the correlation between HbA1c and CFR and IMR. Beta coefficient and its 95 % confidence interval (CI) were reported. Logistic regression analysis was performed to identify the

baseline characteristics associated with CMD in diabetic patients. The associated variables in the univariate analysis ($p \leq 0.1$) were entered into the final multivariate model. Odds ratio (OR) with 95 % CI were reported. A p value < 0.05 (2-sided) was considered statistically significant. Statistical analyses were performed with R software version 4.2.2 (R Foundation, Vienna).

3. Results

3.1. Study population and baseline characteristics

Baseline characteristics and coronary physiology data of 449 patients have been prospectively collected in the BELmicro registry between October 2021 and September 2023 (Bringmans et al., 2024). Patients selected for the current analysis were 402, and 74 were diabetics. Of these, 13 (18 %) patients were treated with insulin. Diabetic patients were older than non-diabetic patients [69 (61, 75) years in diabetics versus 64 (58, 73) years in non-diabetics, p = 0.02] but there was no difference in sex distribution (50 % of male patients in diabetics versus 45 % in non-diabetics, p = 0.4). Diabetic patients were characterized by a higher burden of cardiovascular risk factors with a higher prevalence of hypertension (73 % in diabetics versus 56 % in non-diabetics, p = 0.009) and dyslipidemia (89 % in diabetics versus 64 % in non-diabetics, p < 0.001). Non-invasive investigations showed no difference between the two study groups. Table 1 summarizes the baseline characteristics of the study groups.

Table 1
Baseline characteristics.

	Overall, N = 402	Diabetics, N = 74	Non-diabetics, N = 328	p-Value
Age, years	65 (58, 73)	69 (61, 75)	64 (58, 73)	0.02
Male	183 (46 %)	37 (50 %)	146 (45 %)	0.4
BMI, kg/m^2	27 (24, 30)	30 (26, 34)	26 (24, 30)	<0.001
eGFR, ml/min	82 (68, 90)	85 (70, 92)	81 (68, 90)	0.2
HbA1c, % (n = 51)	6.8 (6.4, 7.4)	6.8 (6.4, 7.4)	–	–
Hypertension	239 (59 %)	54 (73 %)	185 (56 %)	0.01
Dyslipidemia	275 (68 %)	66 (89 %)	209 (64 %)	<0.001
Current smoking	60 (15 %)	10 (14 %)	50 (15 %)	0.5
Family history of CAD	60 (15 %)	10 (14 %)	50 (15 %)	0.7
Non obstructive CAD[a]	362 (90 %)	69 (93 %)	293 (89 %)	0.3
Previous myocardial revascularization	84 (21 %)	13 (18 %)	69 (22 %)	0.5
Atrial fibrillation	73 (18 %)	16 (22 %)	57 (17 %)	0.4
Clinical presentation:				0.7
Asymptomatic	27 (6.7 %)	6 (8.1 %)	21 (6.4 %)	
Typical angina	161 (40 %)	29 (39 %)	132 (40 %)	
Atypical angina	123 (31 %)	22 (30 %)	101 (31 %)	
Dyspnea	81 (20 %)	17 (23 %)	64 (20 %)	
Other	10 (2.5 %)	0 (0 %)	10 (3.0 %)	
Non-invasive investigations:				
ECG repolarization abnormalities	51 (13 %)	6 (8.1 %)	45 (14 %)	0.2
LVEF, % (n = 332)	60 (56, 62)	59 (56, 60)	60 (56, 62)	0.14
Regional wall-motion abnormalities (n = 339)	57 (17 %)	7 (11 %)	50 (18 %)	0.2
Inducible myocardial ischemia (n = 238)	79 (33 %)	14 (31 %)	65 (34 %)	0.7

Median (IQR); n (%).
ANOCA: angina and non-obstructive coronary artery disease; BMI: body mass index; CAD: coronary artery disease; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention.
[a] Defined by <50 % diameter stenosis on coronary angiography and/or FFR >0.80.

3.2. Physiology measurements and rate of CMD between diabetics and non-diabetics

Most of the procedures were performed through a radial artery access (97 % overall) with a 6 French guiding catheter (95 % overall). Table 2 summarizes the physiology indices measured in patients with and without DM. Among the physiological measurements, median Pd/Pa was comparable between diabetic and non-diabetic patients [0.95 (0.93, 0.96) in diabetics versus 0.95 (0.93, 0.96) in non-diabetics, p = 0.4] as was median FFR [0.92 (0.89, 0.94) in diabetics versus 0.91 (0.88, 0.94) in non-diabetics, p = 0.8]. Median CFR was 3.0 (2.1, 4.4) in diabetics versus 2.8 (2.0, 4.1) in non-diabetics (p = 0.4) (Fig. 1, panel A). IMR was slightly lower in diabetic patients [16 (9, 24) in diabetics versus 18 (12, 27) non-diabetics, p = 0.04] (Fig. 1, panel B), however, the rate of IMR ≥ 25 was comparable between the two groups (23 % in diabetics versus 31 % in non-diabetics, p = 0.2). RRR values were comparable between diabetics and non-diabetics [3.8 (2.4, 5.1) in diabetics versus 3.3 (2.3, 4.7) in non-diabetics, p = 0.2]. There was no difference in prevalence of CMD between the two groups (46 % in diabetics versus 48 % in non-diabetics, p = 0.8). Structural CMD was diagnosed in 16 % of diabetic patients versus 21 % of non-diabetic patients (p = 0.4). Functional CMD was present in 23 % of diabetic patients versus 17 % of non-diabetic patients (p = 0.2). Patients with isolated abnormal IMR were 7.0 % in diabetics versus 10 % in non-diabetics (p = 0.3) (Fig. 2).

3.3. Effects of longstanding diabetes and HbA1c levels on coronary microcirculation

Among diabetic patients, the onset time of DM was known in 62 patients. Of these, 25 had a longstanding diabetes (≥10 years) and 37 had a more recent diagnosis of DM (<10 years). Median HbA1c values were comparable between patients with and without longstanding

Table 2
Results of the coronary physiology assessment.

	Overall, N = 402	Diabetics, N = 74	Non-diabetics, N = 328	p-Value
Pd/Pa	0.95 (0.93, 0.96)	0.95 (0.93, 0.96)	0.95 (0.93, 0.96)	0.4
FFR	0.92 (0.88, 0.94)	0.92 (0.89, 0.94)	0.91 (0.88, 0.94)	0.8
Resting Tmn, s	0.66 (0.45, 0.94)	0.59 (0.44, 0.89)	0.67 (0.46, 0.96)	0.2
Hyperemic Tmn, s	0.23 (0.14, 0.35)	0.19 (0.12, 0.33)	0.23 (0.15, 0.35)	0.05
CFR	2.9 (2.0, 4.1)	3.0 (2.1, 4.4)	2.8 (2.0, 4.1)	0.4
CFR < 2.5	152 (38 %)	29 (39 %)	123 (38 %)	0.8
IMR	18 (11, 26)	16 (9, 24)	18 (12, 27)	0.04
IMR ≥ 25	119 (30 %)	17 (23 %)	102 (31 %)	0.2
RRR	3.4 (2.3, 4.7)	3.8 (2.4, 5.1)	3.3 (2.3, 4.7)	0.2
CMD	191 (48 %)	34 (46 %)	157 (48 %)	0.8
Structural CMD	80 (20 %)	12 (16 %)	68 (21 %)	0.4
Functional CMD	72 (18 %)	17 (23 %)	55 (17 %)	0.2
Abnormal IMR	39 (10 %)	5 (7 %)	34 (10 %)	0.3

Median (IQR); n (%).
CFR: coronary flow reserve; CMD: coronary microvascular dysfunction; FFR: fractional flow reserve; IMR: index of microcirculatory resistance; Pa: mean aortic pressure; Pd: mean distal pressure; Tmn: mean transit time; RRR: resistive reserve ratio.

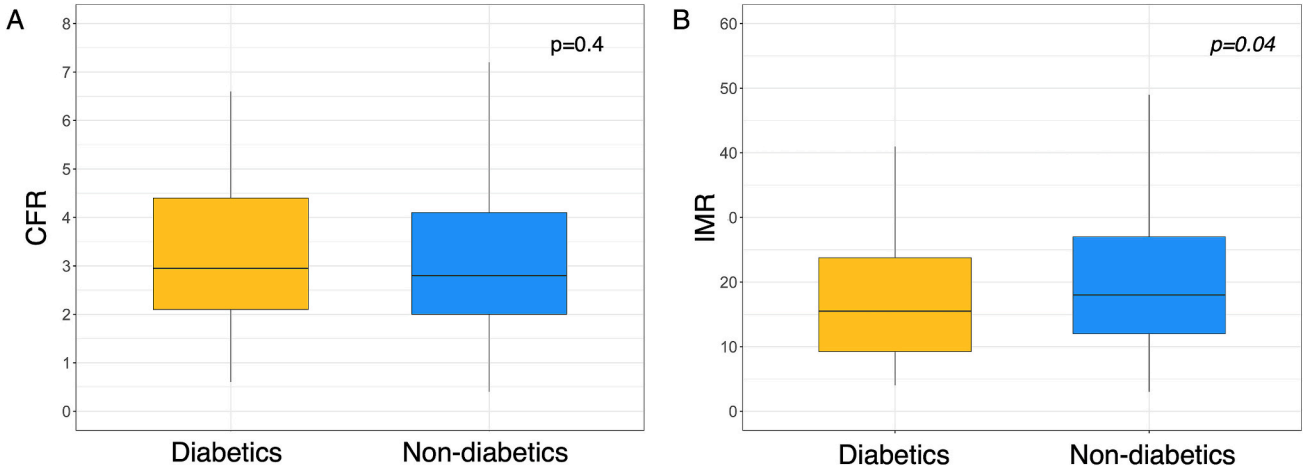

Fig. 1. Distribution of CFR and IMR values in diabetic and non-diabetic patients.
Boxplots showing the distribution of CFR (panel A) and IMR (panel B) values in diabetics and non-diabetics.
CFR: coronary flow reserve; IMR: index of microcirculatory resistance.

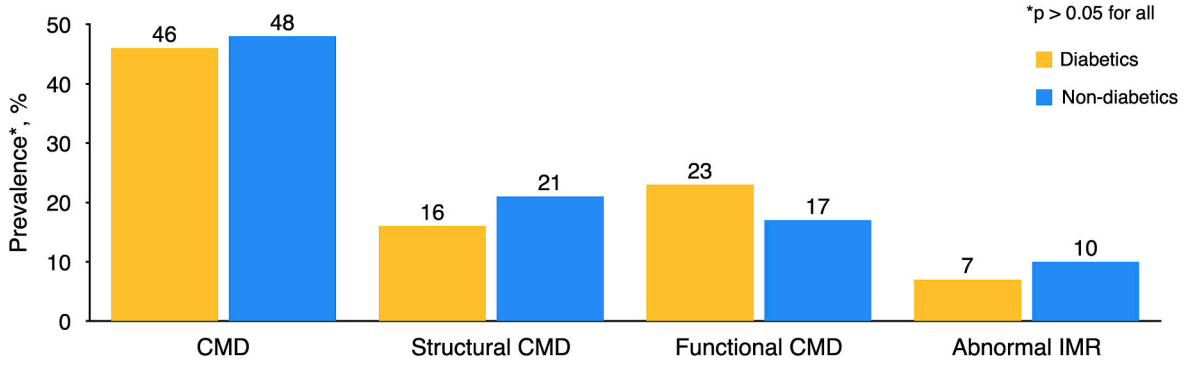

Fig. 2. Prevalence of CMD in diabetic and non-diabetic patients.
Bar plots showing the rates of CMD, structural CMD, functional CMD and isolated abnormal IMR in diabetics and non-diabetics.
CMD: coronary microvascular dysfunction; IMR: index of microcirculatory resistance.

diabetes [7.00 % (6.40–7.50) in patients with longstanding diabetes versus 6.70 % (6.30–7.40) in patients with recent diagnosis, p = 0.4], confirming the excellent glycemic control in the longstanding group. CFR and IMR values were comparable between patients with longstanding diabetes and patients with recent diagnosis [CFR: 2.8 (2.2, 3.4) in the longstanding group versus 3.5 (2.1, 4.9) in the recent diagnosis group, p = 0.2 and IMR: 16 (10,31) in the longstanding group versus 15 (8, 21) in the recent diagnosis group, p = 0.4] (Fig. 3, panels A and B). No significant differences were found in the prevalence of CMD and its endotypes between the two subgroups of diabetic patients (Table 3). HbA1c levels before the coronary physiology assessment were available in 51 patients. No significant correlations were found between HbA1c levels and CFR (beta coefficient: 0.06, 95 % CI: −0.56 to 0.68, p = 0.8) and IMR (beta coefficient: -0.87, 95 % CI: −5.55 to 3.80, p = 0.7) (Fig. 3, panels C and D).

Predictors of CMD in patients with diabetes mellitus. Univariate and multivariate analyses showed that female sex was the only independent predictor of CMD in diabetic patients. (Table 4).

4. Discussion

The main findings of the current study can be summarized as follows: 1) the prevalence of CMD was comparable between diabetic patients and non-diabetic patients; 2) the rates of functional and structural CMD were similar in patients with and without DM; 3) longstanding diabetes and HbA1c levels were not associated with CMD; 4) the presence of concomitant cardiovascular risk factors was not associated with CMD, while female sex was the only independent predictor of CMD in diabetic patients.

Metabolic disorders associated with DM are responsible for endothelial and microvascular dysfunction in several organs, including the heart (Crea et al., 2022). Previous non-invasive studies have shown a higher rate of CMD in diabetic patients (Yokoyama et al., 1997; Pitkänen et al., 1998; Sezer et al., 2016; Atar et al., 2012). However, previous studies that aimed to assess coronary physiology using invasive methods revealed conflicting results (Gallinoro et al., 2021; Hwang et al., 2021; Leung and Leung, 2016; Picchi et al., 2011; Melikian et al., 2007; Chitturi et al., 2025). Therefore, whether invasive coronary physiology assessment can confirm or not the higher prevalence of CMD in diabetics remained a matter of debate. Our study sheds further light on the coronary microvascular function of this specific patients' population and is the first to investigate potential associations between glycated hemoglobin, diabetes duration and the presence of CMD. Our analysis was conducted in a real-world population of patients undergoing coronary physiology assessment and showed no difference in rates of CMD and its endotypes between diabetics and non-diabetics. As a matter of fact, our CFR results were similar to those reported by Melikian et al., whose study proved no difference in CFR values between diabetic and non-diabetic patients (Melikian et al., 2007). The authors hypothesized that diabetic patients may be predominantly affected by endothelial dysfunction, which could have been detected in our study population with the administration of an endothelium-specific agonist such as

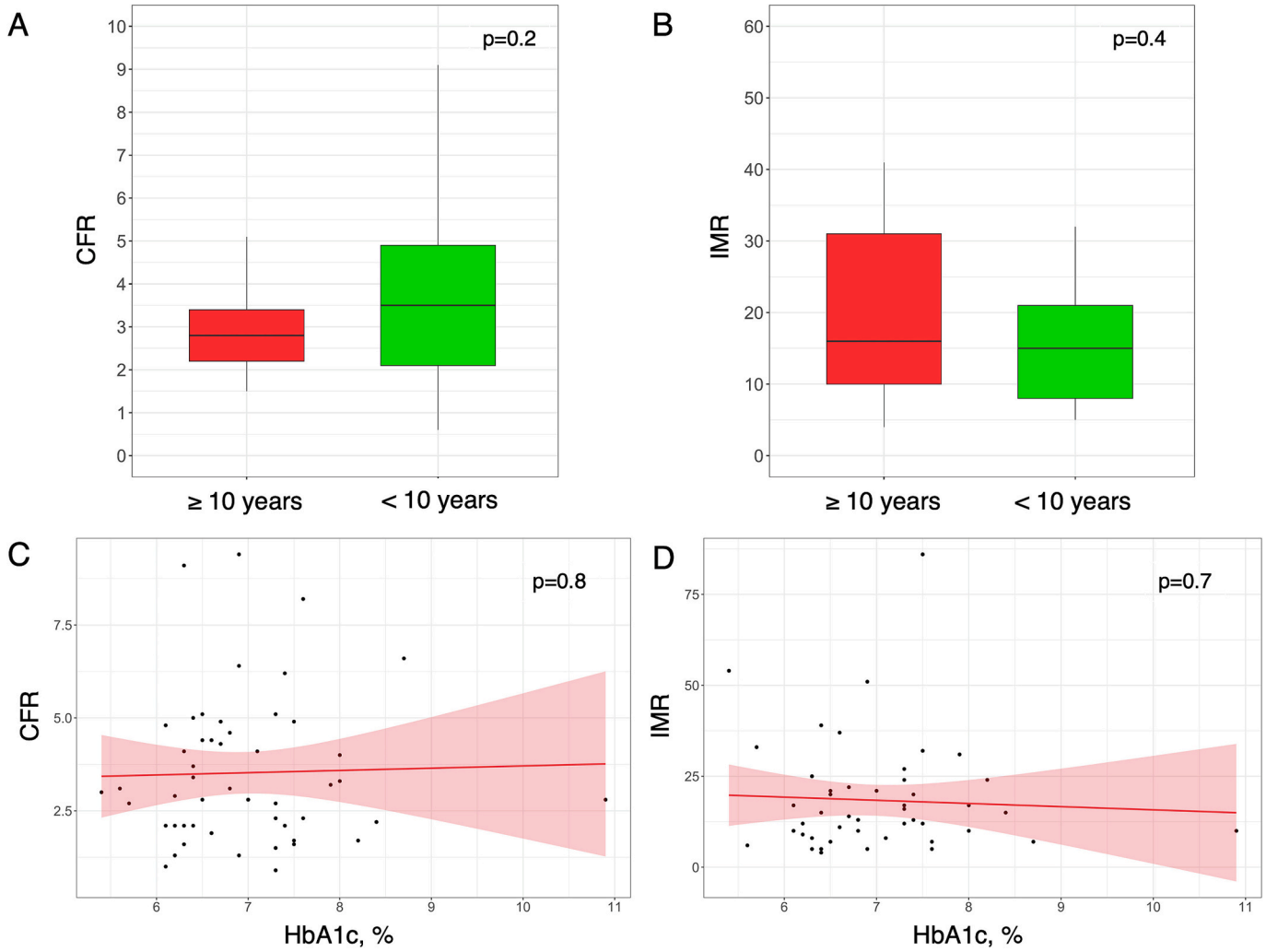

Fig. 3. Association between diabetes duration and HbA1c levels and CMD.
Boxplots showing the distribution of CFR (panel A) and IMR (panel B) values in patients with longstanding diabetes and those recently diagnosed.
Scatterplots showing the correlation between HbA1c levels and CFR (panel C) and IMR (panel D).
CFR: coronary flow reserve; HbA1c: glycated hemoglobin; IMR: index of microcirculatory resistance.

Table 3
Results of coronary physiology assessment in patients with and without long-standing diabetes.

	Diabetes ≥10 years N = 25	Diabetes <10 years N = 37	p-Value
Pd/Pa	0.95 (0.92, 0.96)	0.95 (0.93, 0.96)	0.5
FFR	0.91 (0.88, 0.93)	0.92 (0.90, 0.94)	0.2
Resting Tmn, s	0.58 (0.43, 0.90)	0.62 (0.46, 0.82)	>0.9
Hyperemic Tmn, s	0.20 (0.12, 0.34)	0.17 (0.12, 0.29)	0.4
CFR	2.8 (2.2, 3.4)	3.5 (2.1, 4.9)	0.2
IMR	16 (10, 31)	15 (8, 21)	0.4
RRR	3.3 (2.4, 4.2)	4.5 (2.6, 6.0)	0.1
CMD	13 (52 %)	13 (35 %)	0.2
Structural CMD	5 (20 %)	5 (14 %)	0.5
Functional CMD	5 (20 %)	7 (19 %)	>0.9
Abnormal IMR	3 (12 %)	1 (2.7 %)	0.3

Median (IQR); n (%).
CFR: coronary flow reserve; CMD: coronary microvascular dysfunction; FFR: fractional flow reserve; IMR: index of microcirculatory resistance; Pa: mean aortic pressure; Pd: mean distal pressure; Tmn: mean transit time; RRR: resistive reserve ratio.

Table 4
Univariate and multivariate analyses for predictors of CMD in diabetic patients.

	OR	95 % CI	p-Value	OR	95 % CI	p-Value
Age	1.04	0.99, 1.10	0.1	1.02	0.96, 1.09	0.5
Female sex	3.06	1.20, 8.12	0.02	2.71	1.02, 7.50	0.049
BMI	1.00	0.90, 1.10	0.9			
eGFR	0.98	0.95, 1.00	0.1	0.98	0.95, 1.01	0.2
Hypertension	0.80	0.28, 2.25	0.7			
Dyslipidemia	2.82	0.60, 20.24	0.2			
Current smoking	0.63	0.15, 2.30	0.5			
Non obstructive CAD[a]	0.19	0.01, 1.38	0.2			
LVEF	1.00	0.95, 1.06	0.9			
HbA1c	0.85	0.42, 1.59	0.6			
Diabetes ≥ 10 years	2.0	0.71, 5.74	0.2			

BMI: body max index; CAD: coronary artery disease; CI: confidence interval; eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin; LVEF: left ventricular ejection fraction; OR: odds ratio.
[a] Defined by <50 % diameter stenosis on coronary angiography and/or FFR >0.80.

acetylcholine. Therefore, a complete coronary function testing, including vasoreactivity test, should be preferred to assess both non-endothelial and endothelial pathways of CMD (Kunadian et al., 2020). Hwang et al. demonstrated that diabetic patients were characterized by lower CFR compared to non-diabetics, however, the CFR values of this large study may have been hampered by the presence of lower FFR values in the diabetic group. In addition, mean CFR of both diabetic and non-diabetic patients resulted in the normal range, while the rate of diabetic patients with abnormal CFR values was not reported (Hwang et al., 2021). The same findings were observed in the study by Leung et al., where CFR values were lower in diabetic patients, but still in the normal range (Leung and Leung, 2016). Moreover, Hwang et al. and Picchi et al. demonstrated comparable IMR values between diabetic and non-diabetic patients (Hwang et al., 2021; Picchi et al., 2011). This is partially consistent with the results of our study, which showed slightly lower IMR values in diabetic patients, while the rate of abnormal IMR was comparable to the non-diabetic group. Only Leung et al. found higher IMR values in diabetic patients, but these results may have been influenced by the small number of patients included in the study (Leung and Leung, 2016). Interestingly, some authors have shown that the lower CFR values in diabetics are mainly due to increased resting coronary flow (Picchi et al., 2011; Meyer and Schwaiger, 1997). On the contrary, other studies have proved that the lower CFR values are determined by reduced hyperemic coronary flow (Yokoyama et al., 1997; Nahser et al., 1995). None of these hypothesis can be confirmed in our study, since resting Tmn measurements were comparable between diabetic and non-diabetic patients, and hyperemic Tmn values were even slightly lower in diabetics. As a consequence, no differences in the rates of functional and structural CMD were found between the two groups.

Sezer et al. evaluated the coronary microvascular function in diabetic patients using transthoracic echocardiography and suggested that the pathophysiological mechanisms of DM may impair the coronary microvascular function in a time-dependent manner. Specifically, they hypothesized that DM may determine an early functional microvascular impairment, which over time may evolve into structural microvascular dysfunction (Sezer et al., 2016). In their study, patients with DM for less than 10 years had higher resting coronary flow, whereas patients with DM for more than 10 years had lower coronary flow and higher microvascular resistance during hyperemia. This theory was not confirmed in our analysis, as both resting and hyperemic transit time measurements and rates of structural and functional CMD were comparable between patients with longstanding diabetes and those recently diagnosed. Notably, despite the fact that approximately one third of patients had been affected by longstanding diabetes, the median HbA1c values indicated effective glycemic control in patients with and without longstanding diabetes. This can be hypothesized as the reason for the comparable rate of CMD to the non-diabetic group. However, no significant correlation was observed between HbA1c levels and the presence of CMD in linear regression and multivariate analyses.

The association between cardiovascular risk factors and CMD has been frequently described in the literature, as the pathophysiological mechanisms involved in the development of CAD may also play a role in the development of CMD (Crea et al., 2022). Leung et al. showed that dyslipidemia, hypertension, higher body mass index and scarce glycemic control were predictors of higher IMR values in patients with DM. Nevertheless, large studies investigating the characteristics of different CMD endotypes have reported no differences in the distribution of cardiovascular risk factors, including DM, across different microvascular function groups (Boerhout et al., 2022; Lee et al., 2016). Additionally, a recent study by Zornitzki et al., which was conducted on a large cohort of patients undergoing invasive coronary physiology assessment, demonstrated no association between CMD and traditional coronary atherosclerosis risk factors (Zornitzki et al., 2024). These observations are consistent with our results, which revealed comparable prevalence of CMD between diabetic and non-diabetic patients, despite the higher burden of cardiovascular risk factors in the diabetic group. To further support these findings, multivariate analysis proved that there was no association between the common cardiovascular risk factors and the presence of CMD in the diabetic population. Only female sex appeared to be an independent predictor of CMD among diabetics.

4.1. Study limitations

Some limitations of the current study need to be mentioned. First, the inferential analysis may have been limited by the relatively small number of patients included in the study. Second, given the observational nature of the study, a selection bias cannot be excluded and the results should be interpreted as hypothesis-generating. Third, comprehensive coronary functional testing, including the administration of endothelium-specific agonists to diagnose microvascular angina and epicardial vasospasm, was not systematically performed in all patients included in the BELmicro registry. Therefore, the prevalence of CMD may be underestimated because the endothelium-dependent pathway of CMD has not been studied. Fourth, the diagnosis of CMD was determined by the presence of abnormal CFR and/or abnormal IMR. Nevertheless, it is still unclear whether isolated abnormal IMR represents a true pathological entity. Fifth, several conditions such as underlying cardiomyopathies may affect coronary microvascular function. However, their investigation was outside the scope of the current study, and these data were not collected in the registry. Sixth, antidiabetic treatment strategies may differ among patients in the diabetic groups, and data on diabetic complications such as retinopathy or nephropathy were unavailable. Nevertheless, given the HbA1c levels indicating effective glycemic control, we can hypothesize that the rate of diabetic complications was very low in the diabetic group. Furthermore, multivariate analysis demonstrated no association between HbA1c levels, kidney function and the presence of CMD. Seventh, core-laboratory analysis was not included in the study protocol, but experienced operators performing the coronary physiology assessments reviewed the coronary physiology data reported in the registry. Eight, follow-up data of the study groups were not yet available. Further studies are warranted to provide more information on the prognostic impact of CMD in diabetics.

5. Conclusions

Among patients who underwent clinically indicated coronary physiology assessment, diabetic patients had a similar rate of CMD to non-diabetic patients, despite being older and having a higher prevalence of cardiovascular risk factors. Furthermore, the distribution of functional and structural CMD was comparable between the diabetic and non-diabetic populations. Longstanding diabetes, glycemic control and other concomitant cardiovascular risk factors were not associated with the presence of CMD in diabetic patients.

CRediT authorship contribution statement

Alice Benedetti: Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tijs Bringmans:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Maarten Vanhaverbeke:** Writing – review & editing, Visualization, Validation, Investigation, Data curation. **Frédéric Daniel Mathieu:** Writing – review & editing, Visualization, Validation, Investigation, Data curation. **Pieter-Jan Palmers:** Writing – review & editing, Visualization, Validation, Investigation, Data curation. **Patrick Coussement:** Writing – review & editing, Visualization, Validation, Investigation, Data curation. **Kenneth De Wilder:** Writing – review & editing, Visualization, Validation, Investigation, Data curation. **Bert Everaert:** Writing – review & editing, Visualization, Validation, Investigation, Data curation. **Mathieu Coeman:** Writing – review & editing,

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Vincent F.M. Segers reports a relationship with Research Foundation Flanders that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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