Advances in Medical Sciences 64 (2019) 195–201

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Original research article

Insulin-like growth factor-binding protein 7 (IGFBP 7) as a new biomarker in coronary heart disease

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ARTICLE INFO

Keywords:
Carotid intima-media thickness
Coronary artery disease
Insulin-like growth factor-binding protein-7 (IGFBP-7)
Myocardial infarction

ABSTRACT

Purpose: The role of insulin-like growth factor-binding protein-7 (IGFBP-7) in atherosclerosis is still not well-known. The objective of this study was to find out the following: 1) whether IGFBP-7 may act as a biomarker of coronary artery disease (CAD) occurrence and extent; 2) whether IGFBP-7 is potentially related to the classical and new markers of cardiovascular risk (carotid intima-media thickness - cIMT); 3) whether IGFBP-7 may be a marker of mortality in the group of patients with myocardial infarction (MI).
Materials/Methods: The study group consisted of 212 patients with MI and 75 patients with stable CAD, the control group included 100 healthy volunteers. IGFBP-7 serum concentration was measured.
Results: IGFBP-7 value was considerably higher in the study group (MI and CAD patients - 35.1 ng/ml ($P = 0.000001$) and 32.7ng/ml ($P = 0.0001$), respectively), than in the controls – 25.2ng/ml. No statistically significant differences between IGFBP-7 concentrations in the MI and CAD group were found. No relationship between IGFBP-7 and the coronary lesions advancement in the study group was observed. No changes in IGFBP-7 concentration in the MI patients during hospitalization were observed. In the group of MI patients who died during follow-up, a considerably higher cIMT values were found whereas no statistically significant difference was observed in relation to IGFBP-7 (34.6 *vs.* 35.2 ng/ml).
Conclusions: IGFBP-7 is a good biomarker of CAD occurrence but not of its advancement. We demonstrated the existence of the relation between higher IGFBP-7 concentration and the selected classical risk factors of cardiovascular events as well as cIMT values. IGFBP-7 cannot serve as a marker of acute ischemia. Also, IGFBP-7 was not confirmed as a predictor of mortality in the MI patients.

1. Introduction

Insulin-like growth factor-binding protein-7 (IGFBP-7), which is also called mac25, tumor adhesion factor (TAF), prostacyclin-stimulating factor (PSF), angiomodulin and IGFBP-related protein 1, is a secreted protein, one of the IGFBP-related proteins (IGFBP-rP). IGFBP-7 competes with the insulin-like growth factor 1 (IGF-1) and inhibits its binding to the IGF receptor [1]. Although it shares high homology with the IGFB-rPs and binds IGF-1 and insulin, its binding affinity for IGF-1 is lower than that of IGFBP-1 to -6 [2].

IGFBP-7 is expressed in multiple normal tissues including peripheral nerves, gastrointestinal tract, urinary bladder and prostate as well as breast tissue and specific cell types in kidney, adrenal gland, and skeletal muscle [3]. IGFBP-7 is also highly expressed in the vasculature, where it appears to be able to regulate angiogenesis in conjunction with other factors, including von Willebrand factor [4]. Moreover, this protein has been associated with many physiologic processes, including cell proliferation, adhesion, senescence, apoptosis, and angiogenesis. It is also known to be a tumor suppressor in multiple malignancies [5]. Recently, Kashani et al. [6] reported IGFBP-7 in conjunction with TIMP-2 as a new biomarker for acute kidney injury.

IGFBP-7 has been recently identified as a potential novel prognostic biomarker for HF with reduced ejection fraction. Furthermore, it shows significant links to the presence and severity of echocardiographic parameters of abnormal diastolic function [7]. This protein was associated with cardiac hypertrophy and was expressed at high levels in HF patients [8]. Elevated serum IGFBP-7 levels are associated with insulin resistance and the risk of metabolic syndrome. Compared to other IGFBPs, the affinity of IGFBP-7 to insulin is 500-fold higher. This suggests IGFBP-7 could compete with insulin receptors for insulin binding

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https://doi.org/10.1016/j.advms.2018.08.017
Received 21 December 2017; Accepted 31 August 2018
Available online 13 February 2019

and interfere with the physiological response to insulin, contributing to insulin resistance and subsequently to the development of diabetes and cardiovascular disease [9]. As yet, nothing is known about the role of IGFBP-7 in atherosclerosis advancement. There are no data to determine whether IGFBP-7 may be a new biomarker of both the occurrence and the progress of coronary atherosclerosis, or whether it may have a prognostic value in patients after myocardial infarction.

1.1. The aim of the study

The objective of the study was to assess if IGFBP-7 may act as a biomarker of coronary artery disease (CAD) occurrence and whether it may be linked with a degree of its extension. What is more, we evaluated the relation between IGFBP-7 and classical and new markers of cardiovascular risk, mostly carotid intima-media thickness measurement (cIMT). We separately analyzed patients with MI and stable CAD to investigate hypothesis whether IGFBP-7 is involved in atherosclerotic plaque vulnerability and could be a marker of acute ischemia. We have also examined whether IGFBP-7 may be a predictor of mortality in the group of MI patients.

2. Material and methods

2.1. The study population

Two hundred and twelve acute myocardial infarction (AMI) patients qualified for the invasive treatment and admitted to the Department of Cardiology between 2011 and 2013 were prospectively evaluated. The inclusion criteria were: age (from 18 to 75 years of age), performed coronary angiography, transthoracic echocardiography (TTE) and carotid arteries ultrasound examinations. In all study patients clinical as well as biochemical risk factors of atherosclerosis were assessed. The exclusion criteria were: cardiogenic shock, acute hemodynamic decompensation due to heart failure and severe renal failure (V stage according to the KDIGO guidelines). Of all analyzed patients, 132 (62.3%) were diagnosed with ST-elevation MI (STEMI) and 80 (37.7%) – with non-ST-elevation MI (NSTEMI).

The second group of the study patients consisted of 75 individuals with stable CAD, which on the basis of the results of noninvasive stress tests (treadmill test or stress echocardiography), were qualified by the “heart team” for either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Detailed characteristics of the study patients with CAD is provided elsewhere [10].

2.2. The control group

The study patients were compared to the control group, which consisted of 100 healthy, age- and gender-matched individuals (mean age 61.5 ± 7.9 years) without any known risk factors or complaints of cardiovascular diseases, undergoing their periodical checkups at the Medical University Hospital’s Clinic. The detailed description of the control group was published previously [10]. The detailed characteristics of the study groups were shown in Table 1A and 1B.

2.3. Ethical issues

Written informed consent from all participants – both patients and healthy volunteers – has been obtained. The study project was accepted by the Local Bioethics Committee (protocol number: R-I-002/73/2016).

2.4. Biochemical evaluation

The studied material was venous blood drawn during the first 24 h after the patient was admitted to hospital and on the fifth day of the hospitalization. In order to determine troponin I, CRP, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, glucose, creatinine and IGFBP-7 concentration, the blood was drawn to clot in a closed system of the Monovette type (SARSTEDT, Nümbrecht, Germany). Biochemical parameters were designated within 2 h after the material’s collection. The blood samples (5 ml) drawn for IGFBP-7 determination were left at room temperature for 2 h to allow clot formation and then centrifuged at 1000 g for 20 min at room temperature. Freshly prepared supernatant serum was frozen and stored at −80 °C until use. Serum IGFBP-7 (Insulin Growth Factor Binding Protein; USCN Life Science) levels were analyzed using ELISA according to the manufacturer’s instructions. ELISA experiments were carried out using the recommended serum dilution (1:50). The minimum detectable dose of that ELISA kit is less than 0.065 ng/ml. Intra- and inter-assay coefficients of variation was < 10% and < 12%, respectively. IGFBP concentrations were measured in duplicate each day – on the first and fifth day of hospitalization. The obtained results are the mean of two almost identical measurements.

In the group of patients with stable CAD blood samples were collected once at admission (before PCI or CABG). In the control group blood samples were collected during outpatient care visit.

Then IGFBP-7 levels were compared between MI (admission results), CAD and control groups.

Glomerular filtration rate was calculated by Cockroft-Gault formula.

2.5. Echocardiography

Transthoracic echocardiography was performed using Philips iE33 ultrasound device, and 1.6–3.2 MHz frequency harmonic imaging was used. The study was performed in a regular way with standard projections. The detailed description is provided elsewhere [10].

2.6. Coronary angiography

Coronary angiography with standard angiographic projections was performed with preferred radial access. The detailed description is published elsewhere [10].

2.7. Doppler ultrasonography of the carotid arteries

The assessments of the common carotid artery (CCA) and carotid bulb (CB) were performed with Philips iE33 B-mode ultrasound device as described elsewhere [11]. The presence of atherosclerotic plaques as well as intima-media thickness (IMT) measurements were evaluated. The definition of a plaque was IMT of more than 1.5 mm [12,13].

2.8. Statistical analysis

The mean values and standard deviations for quantitative variables as well as the quantitative and percentage distribution for qualitative variables were calculated. Pearson's correlation coefficient for categorical variables of normal distribution and Spearman's correlation coefficient for variables not satisfying normal distribution criteria were calculated. To compare the groups, the statistical analysis of normal distribution variables estimated with the use of the Kolmogorov compatibility test was carried out using the unpaired Student's test and the Mann-Whitney test for variables inconsistent with a normal distribution. The comparison of qualitative variables between the groups was performed using the Chi2 test. P value of < 0.05 was considered statistically significant. A multivariable analysis of the examined parameters has also been performed based on the model of multilogistic regression analysis using a stepwise approach. The statistical analysis was carried out using Statistica 12.0 PL software.

Table 1A
Patients characteristics.

	STEMI group (n = 132)	NSTEMI group (n = 80)	Control group (n = 100)	p value control group vs MI group	CAD group (n = 75)	p value control group vs CAD group	p value MI group vs CAD group
Age (y)	63.8 ± 8.9	62.7 ± 10.8	61.5 ± 7.9	NS	64.0 ± 7.4	NS	NS
Sex women	24 p. (18.2%)	21 p. (26.3%)	33p.(33%)	NS	25 p.(33.3%)	NS	NS
men	108 p. (81.8%)	59 p. (73.7%)	67p.(67%)	NS	50 p.(66.6%)	NS	NS
BMI, kg/m2	27.5 ± 3.6	27.2 ± 3.0	26.9 ± 3.4	NS	28.6 ± 3.7	NS	NS
Smoking (n)	86 p. (65.2%)	52 p. (65%)	28 p. (28%)	$P < 0.001$	51 p. (68%)	$P < 0.001$	NS
Hypertension (n)	84 p. (63.6%)	42 p. (52.5%)	0 p.		60 p.(80%)		$P < 0.01$
Diabetes t.2 (n)	33 p. (26%)	10 p. (12.5%)	0 p.		28 p.(37.3%)		$P < 0.05$
Hiperlipidemia (n)	47 p. (35.6%)	32 p. (40%)	0 p.		49 p.(65.3%)		$P < 0.001$
Systolic BP, mmHg	143.6 ± 22.7	144.2 ± 25.5	132.8 ± 19.0	$P < 0.05$	135.1 ± 19.4	NS	$P < 0.05$
Diastolic BP, mmHg	88.7 ± 16.0	86.8 ± 14.5	83.0 ± 8.0	NS	75.4 ± 12.8	$P < 0.001$	$P < 0.001$
Total cholesterol, mmol/l	4.87 ± 1.1	4.82 ± 1.3	4.4 ± 0.9	$P < 0.05$	4.50 ± 1.0	NS	$P < 0.05$
LDL-cholesterol, mmol/l	3.09 ± 0.9	3.10 ± 1.1	2.74 ± 0.8	$P < 0.05$	2.72 ± 0.9	NS	$P < 0.05$
HDL-cholesterol, mmol/l	1.14 ± 0.3	1.17 ± 0.3	1.6 ± 0.35	$P < 0.05$	1.2 ± 0.3	$P < 0.05$	NS
TG, mmol/l	1.59 ± 0.9	1.62 ± 1.0	1.42 ± 0.54	NS	1.68 ± 0.9	NS	NS
Glucose, mmol/l	6.9 ± 2.5	6.7 ± 2.3	5.65 ± 1.1	$P < 0.05$	6.5 ± 2.1	$P < 0.05$	NS
Creatinine, μmol/l	90.4 ± 47.0	95.2 ± 41.8	89.2 ± 14.8	NS	82.5 ± 30.3	NS	NS
GFR, ml/min	85.4 ± 26.7	82.7 ± 25.5	109.5 ± 30.0	$P < 0.01$	93.8 ± 24.3	$P < 0.05$	$P < 0.05$
Hemoglobin, mmol/l	8.5 ± 0.9	8.4 ± 0.9	8.9 ± 1.0	NS	7.5 ± 1.2	$P < 0.0001$	$P < 0.0001$
EF, %	44.5 ± 8.5	45.6 ± 9.8	55.0 ± 12.5	$P < 0.01$	49.6 ± 7.5	$P < 0.01$	$P < 0.05$
1-vessel disease (n)	52 p. (39.4%)	28 p. (35.0%)	_		8 p. (10.6%)		$P < 0.0001$
2-vessel disease (n)	37 p. (28.0%)	20 p. (25.0%)	_		20 p. (26.6%)		NS
3-vessel disease (n)	35 p. (26.5%)	24 p. (30.0%)	_		47 p. (62.6%)		$P < 0.0001$
Type of lesions in coronary arteries:							
Type A	22 p. (16.6%)	12 p. (15.0%)	_		14 p. (14%)		NS
Type B1	27 p. (20.5%)	19 p. (23.8%)	_		28 p. (28%)		NS
Type B2	39 p. (29.5%)	23 p. (28.8%)	_		31 p. (31%)		NS
Type C	40 p. (30.3%)	25 p. (31.3%)	_		27 p. (27%)		NS
Treatment: Aspirin	209 p. (98.6%)				63 p. (84.0%)		$P = 0.00,001$
Clopidogrel	198 p. (93.4%)				16 p. (21.3%)		$P = 0.00,001$
ACE inhibitors	190 p. (90.0%)				7 p. (9.3%)		$P = 0.00,001$
ARBs	5 p. (2.4%)				37 p. (49.3%)		$P = 0.00,001$
Beta-blokers	200 p. (94.3%)				69 p. (92.0%)		$P = 0.29$
MRAs	63 p. (29.7%)				11 p. (14.6%)		$P = 0.002$
Statins	204 p. (96.2%)				69 p. (92.0%)		$P = 0.10$
Diuretics	42 p. (19.8%)				23 p. (30.6%)		$P = 0.06$
Oral antidiabetic	40 p. (18.9%)				9 p. (12.0%)		$P = 0.16$
Insulin	6 p. (2.8%)				4 p. (5.3%)		$P = 0.47$
Oral anticoagulant	4 p. (1.9%)				15 p. (20.0%)		$P = 0.00,001$

BP – blood pressure; STEMI – ST-elevation myocardial infarction; NSTEMI – non ST-elevation myocardial infarction; EF – ejection fraction; GFR – glomerular filtration rate; CAD – coronary artery disease; ARBs –angiotensin II receptor antagonists; MRAs - mineralocorticoid receptor antagonists.

3. Results

3.1. IGFBP-7 measurements

In the study group (MI and CAD patients) IGFBP-7 concentrations were significantly higher as compared to the controls – median 35.1 ng/ml (interquartile range, IQR 23.3–51.9), $P < 0.05$ and 32.7 ng/ml (IQR 17.0–54.5), $P < 0.05$ *vs.* 25.2 ng/ml (IQR 21.1–30.4), respectively (Fig. 1).

No significant differences of IGFBP-7 concentrations between STEMI and NSTEMI patients were found – median 35.2 ng/ml (IQR 22.9–51.8) *vs.* 34.9 ng/ml (IQR 24.7–51.9), P = NS, respectively. In the MI study sub-group of patients, IGFBP-7 concentrations did not differ significantly between the first and the fifth day – for STEMI median 35.2 ng/ml (IQR 22.9–51.8) *vs.* 32.7 ng/ml (IQR 22.5–47.1), and for NSTEMI median 34.9 ng/ml (IQR 24.7–51.9) *vs.* 35.0 ng/ml (IQR 22.7–54.2), P = NS, respectively. No statistically significant differences of IGFBP-7 concentrations between MI and CAD study sub-group were found ($P = 0.27$) (Fig. 1).

The highest sensitivity and specificity for CAD occurrence was IGFBP-7 level ≥ 38.2 ng/ml with c-statistics derived from receiver operating characteristic (ROC) 0.639 (95% confidence interval

Table 1B
Carotid ultrasonography parameters in the study group (STEMI, NSTEMI and CAD patients) and in the control group (healthy volunteers).

	STEMI group (n = 132)	NSTEMI group (n = 80)	Control group (n = 100)	p value (MI patients vs control)	CAD group (n = 75)	p value (CAD patients vs control)
CCA IMT (mm)	1.1 ± 0.3	1.0 ± 0.2	0.6 ± 0.1	$P = 0.00,001$	1.2 ± 0.5	$P = 0.00,001$
CB IMT (mm)	1.9 ± 0.8	2.0 ± 0.9	1.2 ± 0.4	$P = 0.04$	2.2 ± 1.2	$P = 0.006$
Plaque occurrence in CCA	16p. (12.1%)	5p. (6.3%)	0	$P = 0.000001$	19p. (25.3%)	$P = 0.00,001$
Plaque occurrence in CB	86p. (65.2%)	50p. (62.5%)	0	$P = 0.000001$	50p. (67%)	$P = 0.000001$

STEMI – ST-elevation myocardial infarction; NSTEMI – non ST-elevation myocardial infarction; CAD – coronary artery disease; IMT – intima-media thickness; CCA - common carotid artery; CB – carotid bulb.

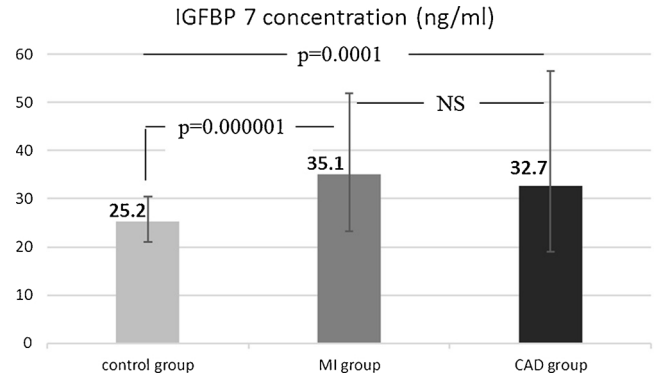

Fig. 1. IGFBP - 7 concentration in the study group (MI and CAD patients) and in the control group (healthy volunteers).

[CI] = 0.588-0.687) in CAD group of patients (Fig. 2A), and IGFBP-7 ≥ 38.7 ng/ml with c-statistics 0.703 (95% CI = 0.648-0.753) (Fig. 2B) in MI group. It has been shown that both IGFBP-7 concentrations and cIMT values are good parameters to differentiate patients with clinical symptoms of CAD. Nevertheless, the measurement of IMT thickness in carotid arteries holds a better predictive value.

The history of hypertension, diabetes and dyslipidemia did not affect IGFBP-7 concentrations in the study sub-groups – neither in the CAD group (P = 0.95), nor MI group (P = 0.47).

Significant, but weak positive correlations of IGFBP-7 and age (r = 0.31, P = 0.004), fibrinogen (r = 0.46, P = 0.01), creatinine (r = 0.13, P = 0.02), CCA IMT values (r = 0.18, P = 0.003) as well as CB IMT values (r = 0.15, P = 0.002) and negative correlations with EF values (r = - 0.12, P = 0.03) in the study group were found.

No significant correlations between IGFBP-7 values and troponin (P = 0.27), lipids (P = 0.28) and glucose (P = 0.69) concentrations

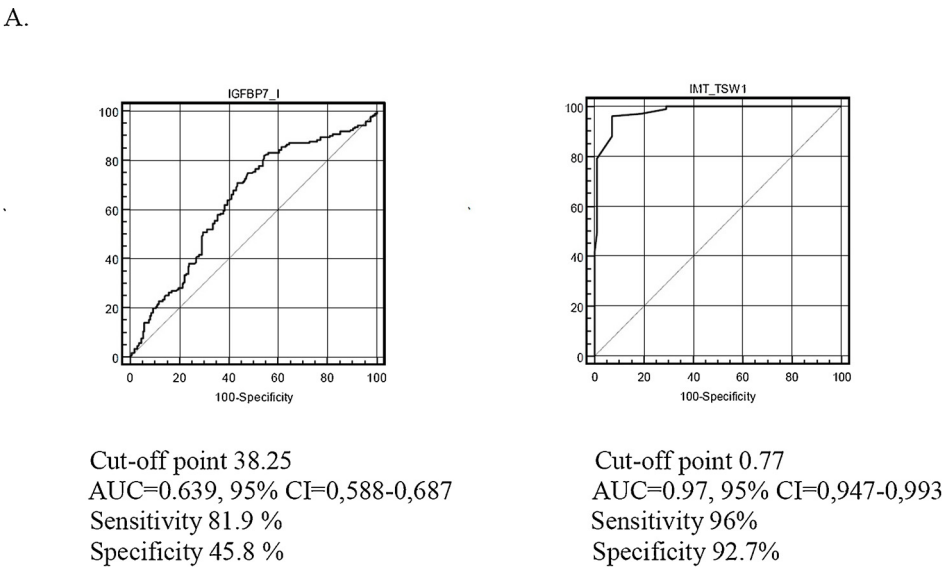

Fig. 2. ROC curve for IGFBP7 concentration and IMT values in common carotid artery in: A. Patients with stable coronary artery disease (CAD group) vs. control group. B. Patients with myocardial infarction (MI group) vs. control group.

Table 1C
Concentration of IGFBP-7 in the study group (MI and stable CAD group) according to pharmacological treatment.

	IGFBP-7 concentration in MI group (ng/ml)			IGFBP-7 concentration in stable CAD group (ng/ml)		
	YES	NO	*P*	YES	NO	*P*
Aspirin	35.1 (23.3-51.5)	41.6 (26.7-56.5)	$P = 0.77$	29.8 (16.9-54.2)	23.6 (21.8-74.1)	$P = 0.54$
Clopidogrel	35.0 (22.6-51.8)	37.1 (24.7-72.7)	$P = 0.67$	28.0 (16.3-65.2)	30.7 (18.2-54.5)	$P = 0.99$
ACE inhibitors	35.3 (23.3-52.9)	26.9 (23.5-41.3)	$P = 0.36$	47.5 (22.3-77.8)	29.8 (17.0-52.4)	$P = 0.39$
ARBs	41.3 (30.1-62.2)	35.0 (23.3-52.2)	$P = 0.52$	33.9 (18.2-100.5)	29.7 (16.9-41.8)	$P = 0.28$
Beta-blockers	35.0 (23.4-51.9)	35.2 (18.8-56.5)	$P = 0.62$	29.8 (16.9-52.0)	52.4 (28.8-57.8)	$P = 0.28$
MRAs	36.5 (21.9-54.2)	34.5 (23.5-51.4)	$P = 0.66$	57.6 (28.6-93.2)	29.8 (17.0-44.4)	$P = 0.15$
Statins	35.2 (23.2-51.9)	34.1 (23.3-56.5)	$P = 0.95$	29.8 (16.6-55.6)	33.9 (23.0-40.5)	$P = 0.63$
Diuretics	34.9 (21.7-47.7)	35.2 (23.6-52.9)	$P = 0.41$	32.0 (14.9-71.8)	29.8 (18.4-43.1)	$P = 0.42$
Oral antidiabetic	33.2 (22.4-49.1)	38.2 (25.3-56.9)	$P = 0.28$	43.7 (29.6-83.7)	29.8 (16.4-52.4)	$P = 0.13$
Insulin	32.2 (23.3-40.6)	35.1 (23.4-52.3)	$P = 0.58$	30.7 (28.6-74.2)	30.3 (17.0-53.8)	$P = 0.47$
Oral anticoagulants	32.8 (26.7-39.2)	35.2 (23.3-52.2)	$P = 0.56$	23.6 (16.4-34.5)	31.5 (18.6-56.6)	$P = 0.27$

MI - myocardial infarction; CAD-coronary artery disease; ARBs –angiotensin II receptor antagonists; MRAs - mineralocorticoid receptor antagonists.

were found.

No statistically significant differences of IGFBP-7 concentrations between the group of patients with low EF (< 50%) and high EF (≥ 50%) were found.

In both study sub-groups of patients, IGFBP-7 concentrations did not differ significantly depending on the used pharmacological treatment (Table 1C).

In the study groups no significant relationships between IGFBP-7 concentrations and the extent of coronary lesions were found (Fig. 3).

3.2. Follow-up in the MI group

During the follow-up which lasted from 2 to 4 years (average period – 2.8 years), the mortality was assigned based upon a uniform period of follow-up - after 2 years. In total 18 patients died in the MI group (8.5%) – 7 patients in NSTEMI group (8.7%) and 11 patients in STEMI group (8.3%), P = NS. Among them, 8 patients died due to subsequent MI, in 6 cases sudden cardiac death occurred, and in 4 patients the cause of death was unclear.

Patients who died were significantly older ($P = 0.003$); they suffered from three-vessel coronary artery disease ($P = 0.03$), were diagnosed with diabetes ($P = 0.009$), chronic kidney disease, or hyperlipidemia ($P = 0.002$) and had a previous episode of an acute coronary syndrome in the medical history ($P = 0.0005$). Higher CCA and CB IMT values in deaths were found – 1.3 ± 0.4 mm *vs.* 1.0 ± 0.3 mm, $P = 0.02$ and 2.3 ± 0.8 mm *vs.* 1.9 ± 0.7 mm, $P = 0.04$, respectively. In the sub-group of MI patients, no statistically significant differences in IGFBP-7 concentrations in deaths as compared to survivors were found (34.6 ng/ml *vs.* 35.2 ng/ml, P = NS).

At the 5% significance level, assuming the effect size of interest equal to the difference of IGFBP-7 log-concentrations observed for control and MI group, and variance estimate pooled from both CAD groups, the type II error probability for two-sided *t*-test was estimated at 0.197 for equinumerous groups of 75 patients, each. Since the actual inference is based on nonparametric statistics due to non-normal distribution of IGFBP-7 levels, the power calculation was performed for log-transformed values.

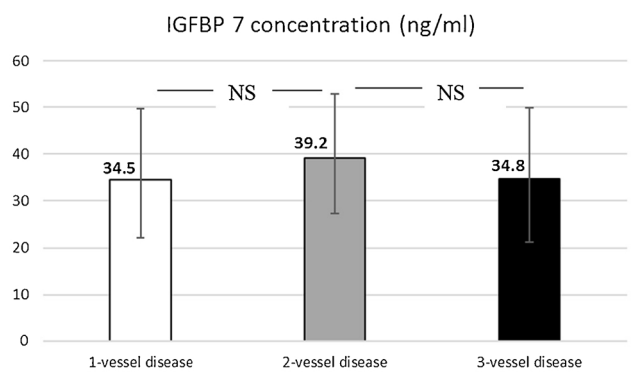

Fig. 3. IGFBP - 7 concentration and a degree of coronary vessels changes advancement in the study group (stable CAD and MI patients).

3.3. Multivariable logistic regression analysis

A multivariable logistic regression analysis using a stepwise approach including age, gender, CCA and CB IMT values as well as plaques occurrence and IGFBP-7 concentrations revealed the following significant variables influencing the appearance of MI: male gender ($P = 0.02$, odds ratio [OR] = 0.093, 95%CI 0.012 – 0.723), IMT in CB > 0.9 mm ($P = 0.0001$, OR = 245.8, 95%CI 30.1–51482), and IGFBP-7 concentration > 38.7 ng/ml ($P = 0.003$, OR = 698.3, 95%CI 8.81–55330.2).

These variables described the analysis model with 98% sensitivity and 94% specificity.

4. Discussion

IGFBP-7 is a biomarker that has recently been associated with heart failure (HF) and cardiac hypertrophy. On the other hand, as far as we know, there are no studies on the role of IGFBP-7 in atherosclerosis advancement. There are no data whether IGFBP-7 may be a new biomarker of both the occurrence and progress of coronary atherosclerosis, if IGFBP-7 involved in atherosclerotic plaque vulnerability and could be marker of acute ischemia or whether it may have a prognostic value in patients after myocardial infarction.

For the first time we examined IGFBP-7 concentration in the group of patients with stable CAD and the group of patients with AMI. We observed that it is statistically significantly higher in the studied group (CAD and MI patients) in comparison to the control group (healthy volunteers). On the other hand, we did not observe any significant differences in IGFBP-7 concentration depending on the kind of MI (STEMI vs. NSTEMI), the time of marking (first vs. fifth MI day), or the form of CAD (stable CAD vs. MI). Moreover, IGFBP-7 concentration did not correlate to high-sensitivity cardiac troponin concentration – thus it supports the claim that elevation of this biomarker in acute coronary syndrome does not appear to result from myocardial cells necrosis.

Due to the lack of data in the literature on the role of IGFBP-7 in coronary disease, we may only refer to the studies carried out for serum IGF-1 levels in this group of patients. Taking into account the fact that IGF-1 exerts its physiological effect through binding a specific receptor which is modulated by IGFBP, this kind of analysis appears appropriate. A cardio-protective role of IGF-1 has been postulated. Researchers observed significant increase of serum IGF-1 levels in patients with "three

vessel disease" and with high score in Gensini scale when compared to those without any narrowing lesions in coronary arteries and 0 Gensini score [14]. Others confirmed that IGF-1 seems to be a positive indicator for severity of CAD assessed by the Gensini score, and thus its concentration may be an important indicator for assessing the extent of coronary artery involvement [15]. On the other hand, Ricketts et al. [16] revealed that IGF-I and IGFBP-3 are unlikely to be importantly involved in the etiology of CAD in human populations. In the present study, we observed that IGFBP-7 is a good biomarker of the presence of atherosclerotic lesions in coronary vessels whereas its concentration does not reflect a degree of CAD advancement (a number of narrowed coronary arteries).

Baseline IGF-1 concentration was lower in subjects developing acute coronary syndrome than in unaffected controls [17]. In the present study we revealed statistically significantly higher IGFBP-7 concentrations in the group of patients with AMI as compared to healthy individuals. High concentrations of the studied biomarker were maintained during the entire hospitalization period (the first and fifth day of the MI). No change in IGFBP-7 concentration in the MI patients during hospitalization may support the view that IGFBP-7 cannot serve as a marker of acute ischemia. The presence of comparably high concentrations of this protein in the group of patients with angiographically confirmed stable coronary disease allows to recognize IGFBP-7 as a good biomarker of the presence of atherosclerotic lesions in coronary vessels.

Based on ROC analysis we demonstrated that cIMT has better predictive value than IGFBP-7 in differentiating healthy controls from CAD or MI patients. However, carotid ultrasound is a technology that requires available resources and experienced ultrasonography specialist. Introduction of a new biomarker that could be measured in blood will facilitate faster diagnostics in patients.

As yet, in contrast to the postulated prognostic role of IGF-1 in myocardial infarction [17], we did not observe a statistically significant difference in IGFBP-7 concentration in the group of MI patients who died during the follow-up.

IGFBP-7 is able to interact with IGF-1 as well as insulin. Previous studies suggest that serum IGFBP-7 levels may be associated with insulin resistance in type 2 diabetes (T2D). The correlation between IGFBP-7 and IGFBP-1 suggests that low IGFBP-7 may be associated with insulin resistance in T2D [18]. In our own studies, serum IGFBP-7 protein levels were similar among nondiabetic subjects, newly diagnosed and treated T2D patients. Gu et al. [18] also achieved similar results.

Moreover, the occurrence of hypertension and dyslipidemia in the medical history as well as blood pressure values and concentration of lipids after hospital admission did not influence IGFBP-7 concentration either. We did not find any comparative studies in the literature.

Earlier studies show that IGFBP-7 was elevated in patients with diabetic cardiomyopathy compared to control [19]. In our present study there were no statistically significant differences in IGFBP-7 concentrations between the group of patients with EF $< 50\%$ and EF $\geq 50\%$, which is distinct from the results of previous observations. It probably results from the fact that the studied group of MI patients did not have heart failure (HF) symptoms at admission whereas IGFBP-7 concentration was marked during the acute MI before post-infarction HF symptoms developed. Moreover, the patients with stable CAD did not report HF symptoms in the medical history whereas EF evaluated in echocardiography was only slightly lower than in the group of healthy individuals.

A significant observation is the connection between IGFBP-7 concentration and IMT values in carotid arteries (cIMT), which are recognized pre-clinical markers of atherosclerosis. Then, perhaps, IGFBP-7 might also be a marker of atherosclerosis in general, not only the CAD in particular. This, obviously, would require additional evidence. It should be noticed, however, that only IMT values, not IGFBP-7 concentrations, increase proportionally to the amount of narrowed coronary arteries.

4.1. Study limitations

The study limitation of our present study is a small size of the study group. It should be emphasized, however, that this is a pilot study carried out for the first time in the group of patients with both stable CAD and acute coronary syndromes.

The role of IGFBP-7 in the evaluation of cardiovascular risk requires further studies.

Finally, the IGFBP-7 cut points used in our study have not been prospectively validated yet and are probably likely to vary from population to population.

5. Conclusions

IGFBP-7 is a good biomarker of CAD occurrence but not its extension. The relation between higher IGFBP-7 concentration and selected classical risk factors of cardiovascular events and cIMT values was found. IGFBP-7 cannot serve as a marker of acute ischemia. Also IGFBP-7 was not confirmed to be a predictor of mortality in the MI patients.

Conflict of interests

The authors declare no conflict of interests.

Financial disclosure

The authors have no funding to disclose.

The authors' contributions

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Funds collection: n/a

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