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The Role of Insulin-Like Growth Factor-1 and Pregnancy-Associated Plasma Protein-A in Diagnosis of Acute Coronary Syndrome and Its Related Morbidities

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Abstract

Introduction: Pregnancy-associated plasma protein-A (PAPP-A) is a metalloproteinase that plays a role in atherosclerotic plaque destabilization. In recent studies, insulin-like growth factor-1 (IGF-1) has been introduced as a mediator of atherosclerosis. PAPP-A and IGF-1 level may be important diagnostic indicators of acute coronary syndrome (ACS).

Objective: The present study tried to assess the diagnostic role of IGF-1 and PAPP-A biomarkers in ACS spectrum.

Methods: The serum level of IGF-1, PAPP-A and troponin I was determined in 121 consecutive patients with ACS. Relationships were assessed by t-test, ANOVA and the non-parametric equivalent. Accuracy of biomarkers was measured by the area under the ROC curve (AUC) and optimal cut-off points to diagnose STEMI and NSTEMI using Youden index.

Results: In patients with acute ST segment elevation myocardial infarction (STEMI), all of these three biomarkers were significantly higher than those in patients with unstable angina (P= 0.028 for IGF-1, P<0.001 for PAPP-A and Troponin-I). Mean level of IGF-1 in patients with renal failure was significantly higher than that in patients without renal failure (137.9±35.1 vs 105.1±46.9, P=0.003), but PAPP-A and serum Troponin-I level had no significant difference in renal failure groups (P>0.05). ROC curve analysis showed that after Troponin-I, PAPP-A was a good discriminator between patients with STEMI and patients with unstable angina (AUC=0.79). Optimum cut-off value for PAPP-A was found to be 89.2 ng/ml, with sensitivity and specificity of 66.7% and 83.8%, respectively.

Conclusion: PAPP-A can be a novel biomarker for both identification of patients with STEMI and risk stratification in patients with ACS.

Key words: Acute Coronary Syndrome; Insulin-Like Growth Factor I; Morbidity; Pregnancy-Associated Plasma Protein-A

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INTRODUCTION

Insulin-like growth factor-1 (IGF-1) and pregnancy-associated plasma protein-A (PAPP-A) are two biomarkers that have been recently considered in the management of patients with acute coronary syndrome (ACS).

IGF-1 is a functional encoded protein produced by IGF-1 gene. IGF-1 has been shown to oppose endothelial dysfunction by interacting with endothelial binding sites leading to nitric oxide production (1, 2). Also, IGF-1 has some anti-inflammatory and vasodilation properties that result in coronary flow preservation (3). Moreover, the atherogenicity effect of IGF-1 has been suggested due to its potential role to induce vascular smooth muscle cell (VSMC) proliferation leading to arterial obstructive lesions (4, 5). However, there are still conflicting results concerning IGF-1 and coronary artery diseases. Some studies suggested that a decreased level of IGF-1 in patient with ST segment elevation myocardial infarction (STEMI) can be used as a diagnostic marker of myocardial necrosis (6, 7). Conversely, some randomized trials reported diagnostic importance of an increased level of IGF-1 in the setting of stent restenosis and lowering IGF-1 levels with somatostatin analogues such as

angiopeptin (8, 9).

PAPP-A is a human protein encoded by PAPP-A gene (10). This agent is a zinc binding metalloproteinase which splits IGF binding proteins (IGFBPs) especially IGFBP-4, therefore with increasing IGFs allowing their actions (11). Circulating PAPP-A has recently been suggested as an independent predictor of next and late adverse cardiovascular events. Moreover, increased activity of PAPP-A has been reported in ACS, hence it is a promising biomarker for risk stratification in these patients (12-15). Clinically, an increase in serum level of PAPP-A has been shown in patients with ACS that may be an indicator for coronary plaques complexity and vulnerability (16). In fact, higher levels of PAPP-A were found in cells and extracellular matrix of the plaques that showed rupture or erosion compared to stable plaques (12). Despite evidence on the potential role of IGF-1 and PAPP-A as a precursor for stimulating or preserving coronary flow and cardiac function, whether the plasma levels of these two biomarkers provide diagnostic information in patients with coronary lesions has remained unclear. The present study aimed to assess the diagnostic role of IGF-1 and PAPP-A biomarkers for a wide spectrum of coronary artery diseases and their correlation with conventional cardiovascular risk factors.

METHODS

Study design and participants

This cross-sectional study was conducted from 2009 until 2010 in Imam Khomeini Hospital of Naghade, affiliated with Urmia University of Medical Science, West Azerbaijan Province. The study was approved by the Institutional Ethics Committee and written informed consent was obtained from the study population.

Study population

All patients diagnosed as ACS based on the American College of Cardiology guideline definitions by considering troponin levels, ECG abnormalities and clinical context (17); hospitalized in cardiac and critical care unit, admitted within one hour after the onset of chest pain were eligible. ACS was diagnosed based on the latest guideline of American College of Cardiology released on 2014 (especially by serum level of troponin I) (17-19). The exclusion criteria were progressive and serious systemic disorders such as liver diseases, overt heart failure, history of major surgeries, pregnancy, known infectious or inflammatory disorders, or malignancies. Sampling was conducted prospectively and consecutively. A total of 145 patients were admitted during the study and 18 were excluded due to the exclusion criteria and 6 were excluded due to incomplete lab data. Finally, 121 patients were included for the analysis.

Definitions

ACS is a spectrum of conditions from unstable angina (UA) to STEMI. UA is a condition in which biomarkers like troponin do not increase. Inversely, myocardial infarction leads to an increase in troponin. According to the American college of cardiology, STEMI is a condition defined with ST segment elevation plus a rise in troponin I levels above > 0.5 ng/mL and NSTEMI is described with positive troponin levels without ST segment elevation (20, 21). Patients were categorized with eGFR lower than 90 mL/min/1.73 m2 as chronic kidney disease (CKD) (22). Left ventricular systolic dysfunction (LVSDF) is qualitatively categorized to severe (<30%), moderate (30-40%), mild (40-50%) and preserved (>50%) stages (23).

Data gathering

Baseline characteristics including demographics, medical history, and troponin indices were collected from hospital records and approved by two cardiologists using a pre-designed checklist.

Venous blood samples were taken from each patient within three hours after the onset of chest pain for routine tests and for measuring serum level of IGF-1 and PAPP-A. Serum level of IGF-1 was determined by the DEMEDITEC IGF-1 600 ELISA Kit (Enzyme-Linked Immunosorbent Assay). Standard range was defined according to the manufacturer's protocol 10 – 600 ng/ml. The DEMEDITEC PAPP-A US ELISA Kit was also used for PAPP-A assay based on the sandwich principle. The assay ranged 0-450 ng/ml. To minimize inter-observer variability, all measurements were followed by a single researcher.

Data analysis

Results are presented as mean ± standard deviation (SD) and median [Interquartile range (IQR)] for quantitative variables and summarized by absolute frequencies and percentages for categorical variables. Quantitative variables are also compared with independent t-test for two groups and one-way ANOVA for more than two groups. We used Mann-Whitney U and Kruskal-Wallis H test for variables with non-normal distribution. Post hoc analysis and correction of error type-I in multiple comparisons were conducted based-on Bonferroni method. Spearman correlation test was applied to determine the correlation between the level of IGF-1, PAPP-A biomarkers and Troponin-I. We used Shapiro-Wilk test and graphical approaches for assessing

normality.

Accuracy of biomarkers was measured by the area under the ROC curve (AUC). ROC analysis was used to choose the optimal cut-off points to diagnose STEMI and NSTEMI using highest values of the Youden index and calculated sensitivity and specificity with 95% confidence interval (CI) for optimal cut-off points. Statistical significance was determined as a p value of ≤ 0.05. All statistical analyses were performed using SPSS software version 22.0 (Armonk, NY: IBM Corp) and STATA version 14 (Stata Corp LLC).

Results

As shown in table 1, among 121 participants, their mean age was 69.09±13.00 years (range: 38 to 95 years) and the majority of them (68%) were male. Of total patients, 25.4% were smokers and more than 20% had no risk factor of hypertension, hyperlipidemia or diabetes mellitus. Almost 56% of the patients with ACS had unstable angina, and severe left ventricle systolic dysfunction (LVSDF) was detected in 17.4% (Table 1).

Table 1: Baseline characteristics of study population

Variable	Frequency (%)
Gender	
Female	38 (31.4)
Male	83 (68.6)
Risk factors	
Hypertension	32 (24.6)
Hyperlipidemia	26 (20)
Smoker	33 (25.4)
Diabetes mellitus	39 (30)
Type of acute coronary syndrome	
Unstable angina	68 (56.2)
NSTEMI	25 (20.7)
Extensive anterior MI	10 (8.3)
Inferior MI	12 (9.9)
Anteroseptal MI	3 (2.5)
Anterolateral MI	2 (1.7)
LV systolic dysfunction	
Preserved EF	1 (0.8)
Mild LVSDF	62 (51.2)
Moderate LVSDF	37 (30.6)
Severe LVSDF	21 (17.4)

MI: Myocardial infarction; NSTEMI: Non-ST segment elevation myocardial infarction; LVEF: Left ventricular ejection fraction

IGF-1 levels and demographic characteristics

No difference was observed in the mean IGF-1 level (ng/ml) between men and women (115.0±48.3 vs 102.6±42.2, p=0.173). Also, no difference was observed in serum level of IGF-1 between hypertensive and normotensive groups (112.3±40.2 vs 110.7±49.0, p=0.866), the groups with and without hyperlipidemia (107.1±46.0 vs 112.2±47.0, p=0.618), smoker and non-smoker groups (117.3±48.9 vs 108.8 ±45.8, p=0.373), and also diabetics and non-diabetics (117.1±43.2 vs 108.3±48.2, p=0.330).

PAPP-A levels and Troponin I, and demographic characteristics

PAPP-A level was significantly higher in male than in female patients [median (IQR): 70.0 (150.0) vs 19.0 (77.0)]. Also, troponin I was higher in male than in female patients and this difference was marginally significant (p=0.054). PAPP-A levels and Troponin-I in patients with or without any risk factor was not significantly different (p>0.05) (Table 2).

Biomarkers and LVSDF

There were no significant differences in serum level of IGF-1 and PAPP-A, and outcome in terms of different stages of LVSDF (P=0.307 and p=0.792 respectively). But Troponin-I was lower in mild LVSDF than moderate and severe LVSDF, and this difference was marginally significant (p=0.093) (Table 2).

Correlation between IGF-1, PAPP-A and Troponin-I

Our study showed direct significant correlation between troponin I and two parameters of IGF-1 (r=0.29, p=0.001) and PAPP-A (r=0.40, p<0.001). Moreover, the correlation between PAPP-A and IGF-1 indicators was direct and significant (r=0.29, p=0.001).

Comorbidities and level of study biomarkers

Twenty-two patients (18.2%) suffered renal failure. Mean level of IGF-1 in patients with renal failure was significantly higher than those without renal failure (137.9±35.1 vs 105.1±46.9, p=0.003). No difference was found in the level of PAPP-A and serum troponin I level between the patients with and without renal failure (p>0.05) (Table 2).

Type of ACS and biomarkers

All assessed biomarkers were significantly associated with the type of ACS (p<0.05). Mean serum level of IGF-1 was 132.1, 109.3 and 104.0 for STEMI, NSTEMI and UA, respectively (p=0.028). In *post hoc* analysis, a significant difference was observed just between UA and STEMI (p= 0.023) and the difference between NSTEMI and STEMI was not significant (p=0.221) (Table 2).

The relationship of PAPP-A and troponin I with type of ACS was also significant (p<0.001). *Post hoc* analysis showed PAPP-A was significantly lower in UA compared to STEMI [Median (IQR): 12.8 (73.3) vs 116.0 (220.0); p<0.001] and NSTEMI [Median (IQR): 12.8 (73.3) vs 108.0 (128.0); p=0.003]. Also, *post hoc* analysis showed Troponin-I was significantly lower in UA compared to STEMI

Table 2: Distribution and association of IGF-1, PAPP-A and Troponin-I with sex, risk factors, LVSDF, renal failure, type of ACS and type of STEMI

Variable	Insulin-like growth factor-1 Mean (SD)	p	Pregnancy-associated plasma protein-A Mean (SD)	p	Troponin-I Mean (SD)	p
Sex						
Male	115.0 (48.3)	0.173	134.2 (185.3)	0.002	0.88 (2.1)	0.054
Female	102.6 (42.2)		48.3 (68.6)		0.35 (1.2)	
Hypertension						
Yes	112.3 (40.2)	0.866	100.2 (183.6)	0.875	0.76 (1.7)	0.939
No	110.7 (49.0)		109.7 (155.8)		0.69 (1.9)	
Hyperlipidemia						
Yes	107.1 (46.0)	0.618	75.4 (84.7)	0.830	1.1 (3.0)	0.712
No	112.2 (47.0)		115.9 (177.8)		0.61 (1.4)	
Smoker						
Yes	117.3 (48.9)	0.373	134.0 (174.4)	0.123	1.1 (2.8)	0.219
No	108.8 (45.8)		97.1 (158.2)		0.57 (1.3)	
Diabetes mellitus						
Yes	117.1 (43.2)	0.330	110.5 (190.5)	0.706	0.58 (1.5)	0.296
No	108.3 (48.2)		105.6 (149.2)		0.78 (2.0)	
Renal failure						
Yes (n=22)	137.9 (35.1)	0.003	142.4 (214.9)	0.294	0.95 (1.8)	0.351
No (n=99)	105.1 (46.9)		99.4 (149.2)		0.66 (1.9)	
LVSDF						
Mild LVSDF	107.0 (42.5)	0.307	95.6 (156.0)	0.792	0.43 (1.0)	0.093
Moderate LVSDF	111.1 (49.7)		119.6 (180.5)		1.1 (2.8)	
Severe LVSDF	125.2 (52.5)		121.6 (158.9)		0.82 (1.7)	
Type of ACS						
STEMI (n=27)	132.2 (58.2)	0.028	184.8 (171.5)	<0.001	1.9 (3.2)	<0.001
NSTEMI (n=25)	109.3 (44.8)		118.6 (125.1)		0.91 (1.6)	
UA (n=68)	104.1 (40.1)		72.8 (163.7)		0.15 (0.44)	
Type of STEMI						
Inferior (n=12)	137.3 (64.5)	0.890	144.6 (117.5)	0.488	1.1 (1.6)	0.475
Antero Septal (n=3)	146.0 (56.1)		298.3 (192.7)		3.0 (2.7)	
Extensive Anterior (n=10)	126.7 (60.9)		220.3 (219.4)		3.0 (4.7)	
Antero Lateral (n=2)	108.2 (12.1)		79.0 (111.7)		0.15 (0.1)	

SD: Standard deviation; LVSDF: left ventricle systolic dysfunction; ACS: Acute coronary syndromes; STEMI: ST segment elevation myocardial infarction; NSTEMI: Non-ST-segment elevation myocardial infarction; UA: Unstable angina

[Median (IQR): 0.01 (0.02) vs 0.56 (2.6); p<0.001] and NSTEMI [Median (IQR): 0.01 (0.02) vs 0.18 (1.1); p<0.001]. But differences of PAPP-A and troponin I level between STEMI and NSTEMI was not significant (p=0.155 and p=0.113, respectively) (Table 2).

Accuracy of biomarkers to predict STEMI and NSTEMI

In the ROC curve, biomarker levels were plotted for their ability to predict STEMI comparing patients with UA. AUC (95% CI) for IGF-1, PAPP-A and Troponin-I was 0.61 (0.48 to 0.74), 0.79 (0.69 to 0.89), and 0.89 (0.82 to 0.96), respectively. So, IGF-1 level was not able to predict STEMI comparing patients with UA (Figure 1). The optimum cut-off value for PAPP-A was found to be 89.2 ng/ml with 67% sensitivity and 84% specificity. The optimum cut-off value for Troponin-I was found to be 0.086 with 85% sensitivity and 87% specificity (Table 3). Also based-on ROC curve, biomarker levels were plotted for their ability to predict NSTEMI comparing patients with UA. AUC (95% CI) for IGF-1, PAPP-A and Troponin-I was 0.50 (0.37 to 0.64), 0.68 (0.55 to 0.82), and 0.86 (0.78 to 0.94), respectively. So, IGF-1 level was not able to predict NSTEMI comparing patients with UA and also,

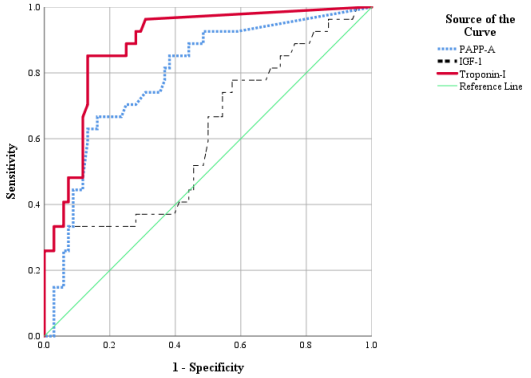

Figure 1: Receiver operator characteristic curve of PAPP-A, IGD-1 and Troponin-I for predict STEMI

Table 3: Optimal cut-off point and accuracy with 95% confidence interval (CI) of PAPP-A and Troponin-I for diagnosis of STEMI and NSTEMI

Biomarker	Classify group	Optimal cut-off point	Sensitivity (95% CI)	Specificity (95% CI)
PAPP-A	STIME-UA	89.2	66.7 (46.0, 83.5)	83.8 (72.9, 91.6)
	NSTIME-UA	95.6	60.0 (38.7, 78.9)	85.3 (74.6, 92.7)
Troponin-I	STIME-UA	0.086	85.2 (66.3, 95.8)	86.8 (76.4, 93.8)
	NSTIME-UA	0.038	87.5 (67.6, 97.3)	80.9 (69.5, 89.4)

PAPP-A had low accuracy for this prediction. The optimum cut-off value for Troponin-I was found to be 0.038 with 88% sensitivity and 81% specificity (Table 3).

Discussion

Although evidence shows the relationship between IGF-1 concentration and different components of metabolic syndrome and cardiovascular risk profile such as body mass index, waist circumference and insulin resistance, the value of this biomarker for predicting cardiovascular events as well as for assessing the type and severity of cardiac ischemic events remains challenging (24-26). As shown in our study, IGF-1 levels were not associated with cardiovascular risk factors. Our results showed serum level of IGF-1 was significantly higher in patients with STEMI than that in patients with UA. *Post hoc* analysis also revealed a significant difference just between UA and STEMI. But, ROC curve analysis for IGF-1 was not significant for predicting STEMI.

It has been previously shown that IGF-1 can enhance ischemic eventuality, and reduce ischemia/reperfusion damage (27). Furthermore, expression of IGF-1 in animal models could protect cardiovascular system from cardiomyocyte death after infarction, and attenuate ventricular dilation, wall stress, and cardiac hypertrophy (28, 29). The controversy between IGF-1 level and cardiac-related events in different studies can be attributed to factors such as probable effect of genetic predisposition. For example, different genetic pathways and upregulation of IGF-1 gene in our population can produce active form of IGF-1. On the other hand, the pathway responsible for activating IGF-1 and its effects on cardiac preconditioning and plaque stability may be suppressed by some factors that should be further assessed.

Regarding IGF-1 and its relationship with ACS and its prognosis, the result of the study by Sekuri et al. showed that significantly decreased levels of IGF-1 in STEMI group of ACS may be used as a diagnostic marker for myocardial necrosis, but since no relationship existed between IGF-1 level and cardiovascular events in 90 days, this parameter cannot be suggested as a negative prognostic factor (6).

Yalcin et al. recently revealed that high IGF-1 levels may identify the patients who are high-risk for stent thrombosis (30).

Interestingly, in patients with renal failure, IGF-1 was significantly higher than that in patients without renal failure. Regarding the effects of IGF-1 on ischemic events and plaque vulnerability, it was higher just in patients with STEMI than that in patients with unstable angina. Several studies propose that IGF-1 is involved in the development of atherosclerosis, and some of its consequences (31, 32).

In the current study, level of IGF-1 was significantly higher in patients with renal failure. Interaction between IGF and kidney disease has been discussed in two recent studies which confirm our results. Bach LA and his colleges showed perturbed regulation of the IGF system in a number of kidney diseases. Enhanced IGF activity was noted in early diabetic nephropathy and polycystic kidneys, but IGF resistance was implicated in chronic kidney failure (33). In a cohort study by Teppala et al., they found higher IGF-1 levels to be positively associated with CKD, and suggested assessment of serum IGF-1 may be valuable for risk stratification of CKD (27).

As presented in our study, it appears that measuring the level of IGF-1 could have a major role in predicting adverse events in patients with ACS especially renal failure. According to our results, the occurrence or uncovering of renal failure as a one of main ACS morbidities can be predicted by high serum levels of IGF-1. Similarly, in Teppala et al. study, higher serum IGF-1 levels were positively associated with CKD after adjusting for age, sex, race/ethnicity, education levels, smoking, alcohol intake, body mass index, diabetes, hypertension and serum cholesterol (27). Thus, it appears that increasing the level of IGF-1 can be helpful to assess tendency to renal failure especially in patients with coronary artery disease.

In our study, there were no significant relationship between PAPP-A level and any of cardiac risk factors. Also, relationship of this biomarker with renal failure was not significant.

In two recent studies conducted by Konev et al. and

Hjortebjerg et al. it was reported that IGFBP-4 fragments from PAPP-A were suggested as a novel biomarker for cardiac risk assessment (33, 34).

The relationship between PAPP-A and coronary angiographic features in patients with ACS was examined in a study by Shehata et al. Higher PAPP-A levels in patients with ACS were associated with unfavorable coronary anatomy and complex angiographic plaque features (35). We were not able to assess angiographic features of study group. Literature review about PAPP-A and ACS or cardiac events shows similar results. In this context, Bonaca et al. conducted a study of usefulness of PAPP-A for risk assessment in NSTEMI. PAPP-A was independently associated with recurrent cardiovascular events in these patients. So, they suggest PAPP-A as a candidate prognostic marker in patients with ACS (36).

Our study revealed a significant association between serum level of PAPP-A and type of ACS and also post hoc analysis showed a significant difference between UA and STEMI. In a similar study by Gururajan et al., PAPP-A had a pivotal role in the pathogenesis of atherosclerosis. PAPP-A level was higher in patients diagnosed as ACS in comparison with the controls. PAPP-A was able to differentiate ischemic and non-ischemic patients. AUC was 0.904, 95% CI (0.874–0.929) with 85% specificity and 90% sensitivity ($P < 0.0001$). The acquired cut-off value was 0.55 µg/mL, and above this value, PAPP-A was regarded to be positive (37). In line with our study, Laterza et al. reported cut-off value of 0.22 mIU/L, with a sensitivity of 66.7% and a specificity of 51.1% for PAPP-A to be a predictor of adverse events at 30 days, but it was inferior to cardiac Troponin-I (38). Detailed clarification of the pathophysiologic role of PAPP-A in detecting STEMI (myocardial necrosis) could be promising for the innovation of specific biomarker-directed therapies.

Limitations

Our study has limitations that warrant consideration. These limitations originate mainly from the inclusion of the in-hospital period without long-term follow-up, failure to consider angiographic data, and lack of a healthy population as the control group. Further studies are recommended for long-term follow-up of patients, comparing IGF-1 and PAPP-A levels between patients with ACS and a control group, analysis of angiographic data including involved coronary artery, Gensini score, syntax score, need to revascularization and finally determining correlation of these parameters with IGF-1 and PAPP-A levels.

Conclusions

In summary, it appears measuring serum level of PAPP-A could predict STEMI in patients with ACS. Serum level of IGF-1 is not able to predict STEMI in cases admitted for ACS. Regarding higher IGF-1 levels in these patients with CKD, this biomarker may be valuable for cardiac risk stratification of CKD, but further studies are necessary to clarify this point.

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Authors' contribution

MM contributed to the concept, design and implementation of the study. MM, JN, BS and AG also contributed in the conception of the work. KHZ and FS agreed for all aspects of the work. BS, MA and LAZ contributed to revising the draft. JZ contributed to analysis of the data and revision of the draft. All the authors checked the final version and approved its content.

Conflict of interest

None declared.

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References

1. Oltman CL, Kane NL, Gutterman DD, Bar RS, Dellsperger KC. Mechanism of coronary vasodilation to insulin and insulin-like growth factor I is dependent on vessel size. Am J Physiol Endocrinol Metab. 2000;279(1):E176-81.

2. Twickler MT, Cramer JM, Koppeschaar HP. Unraveling Reaven's syndrome X: serum insulin-like growth factor-I and cardiovascular disease. Circulation. 2003;107(20):e190-2.

3. Spies M, Nesic O, Barrow RE, Perez-Polo JR, Herndon DN. Liposomal IGF-1 gene transfer modulates pro- and anti-inflammatory cytokine mRNA expression in the burn wound. Gene Ther. 2001;8(18):1409-15.

4. Grant MB, Wargovich TJ, Bush DM, Player DW, Caballero S, Foegh M, et al. Expression of IGF-1, IGF-1 receptor and TGF-β following balloon angioplasty in atherosclerotic and normal rabbit iliac arteries: An immunocytochemical study. Regul Pept. 1999;79(1):47-53.
5. Liu K, Ying Z, Qi X, Shi Y, Tang Q. MicroRNA-1 regulates the proliferation of vascular smooth muscle cells by targeting insulin-like growth factor 1. Int J Mol Med. 2015;36(3):817-24.
6. Sekuri C, Arslan O, Utük O, Bayturan O, Onur E, Tezcan UK, et al. Serum level of insulin-like growth factor-1 and insulin-like growth factor binding protein-3 in acute coronary syndromes and relationship with prognosis. Anadolu Kardiyol Derg. 2004;4(3):209-12.
7. Conti E, Andreotti F, Sestito A, Riccardi P, Menini E, Crea F, et al. Reduced levels of insulin-like growth factor-1 in patients with angina pectoris, positive exercise stress test, and angiographically normal epicardial coronary arteries. Am J Cardiol. 2002;89(8):973-5.
8. Bayes-Genis A, Conover CA, Schwartz RS. The insulin-like growth factor axis a review of atherosclerosis and restenosis. Circ Res. 2000 Feb 4;86(2):125-30.
9. Schini-Kerth VB. Dual effects of insulin-like growth factor-I on the constitutive and inducible nitric oxide (NO) synthase-dependent formation of NO in vascular cells. J Endocrinol Invest. 1999;22(5 Suppl):82-8.
10. Overgaard MT, Haaning J, Boldt HB, Olsen IM, Laursen LS, Christiansen M, et al. Expression of recombinant human pregnancy-associated plasma protein-A and identification of the proform of eosinophil major basic protein as its physiological inhibitor. J Biol Chem. 2000;275(40):31128-33.
11. Kalousová M, Zima T, Krane V, März W, Wanner C, Tesař V, et al. Pregnancy-associated plasma protein A associates with cardiovascular events in diabetic hemodialysis patients. Atherosclerosis. 2014;236(2):263-9.
12. Bayes-Genis A, Conover CA, Overgaard MT, Bailey KR, Christiansen M, Holmes Jr DR, et al. Pregnancy-associated plasma protein A as a marker of acute coronary syndromes. New England Journal of Medicine. 2001;345(14):1022-9.
13. Lund J, Qin QP, Ilva T, Pettersson K, Voipio-Pulkki LM, Porela P, et al. Circulating pregnancy-associated plasma protein a predicts outcome in patients with acute coronary syndrome but no troponin I elevation. Circulation. Circulation. 2003;108(16):1924-6.
14. Heeschen C, Dimmeler S, Hamm CW, Fichtlscherer S, Simoons ML, Zeiher AM, et al. Pregnancy-associated plasma protein-A levels in patients with acute coronary syndromes: comparison with markers of systemic inflammation, platelet activation, and myocardial necrosis. J Am Coll Cardiol. 2005;45(2):229-37.
15. Wu XF, Yang M, Qu AJ, Mintz GS, Yang Y, Shang YP, et al. Level of pregnancy-associated plasma protein-A correlates with coronary thin-cap Fibroatheroma burden in patients with coronary artery disease: novel findings from 3-vessel virtual histology intravascular ultrasound assessment. Medicine (Baltimore). 2016;95(3):e2563.
16. Liu ZY, Zhang JY, Sun TW, Zhang YJ, Zhang L, Wang LX. Levels of pregnancy-associated plasma protein A in patients with coronary artery disease. Clin Invest Med. 2008;31(2):E85-9.
17. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC Guideline for the management of patients with non-ST-elevation acute coronary syndrom: a report of the American Collegen Practice Guidline. J Am Coll Cardiol. 2014;64(24):e139-e228
18. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr,. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevationmyocardial infarction: a report of the American College of Cardiology/American heartassociation Task Force on Practice Guidelines (Writin g Committee to Revise the 2002 Guidelinesfor the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol. 2007;50(7):e1-e157.

19. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidlines. J Am Coll Cardiol. 2013;61(4):485-510.
20. Rapid test for the qualitative determination of Cardiac Troponin I (cTnI) in human whole blood, serum and plasma,2011, available at: www.demeditec.com
21. Baillard C, Boussarsar M, Fosse JP, Girou E, Le Toumelin P, Cracco C, et al. Cardiac troponin I in patients with severe exacerbation of chronic obstructive pulmonary disease. Intensive Care Med. 2003;29(4):584-9.
22. Levey AS, Inker L. Definition and staging of chronic kidney disease in adults. Curhan, GC. 2013.
23. Kim Y, Garvin J, Goldstein MK, Meystre SM. Classification of Contextual Use of Left Ventricular Ejection Fraction Assessments. Stud Health Technol Inform. 2015;216:599-603.
24. Grundy SM, Brewer HB, Cleeman JI, Smith SC, Lenfant C, American Heart Association, et al. Definition of metabolic syndrome report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on scientific issues related to definition. Circulation. 2004;109(3):433-8.
25. Gomez JM, Maravall FJ, Gomez N, Navarro MA, Casamitjana R, Soler J. Interactions between serum leptin, the insulin-like growth factor-I system, and sex, age, anthropometric and body composition variables in a healthy population randomly selected. Clin Endocrinol (Oxf). 2003;58(2):213-9.
26. Aguirre GA, De Ita JR, de la Garza RG, Castilla-Cortazar I. Insulin-like growth factor-1 deficiency and metabolic syndrome. J Transl Med. 2016;14:3.
27. Teppala S, Shankar A, Sabanayagam C. Association between IGF-1 and chronic kidney disease among US adults. Clin Exp Nephrol. 2010;14(5):440-4..
28. Paolisso G, Rizzo MR, Mazziotti G, Tagliamonte MR, Gambardella A, Rotondi M, et al. Advancing age and insulin resistance: role of plasma tumor necrosis factor-α. Am J Physiol. 1998;275(2):E294-9.
29. Davani EY, Brumme Z, Singhera GK, Côté HC, Harrigan PR, Dorscheid DR. Insulin-like growth factor-1 protects ischemic murine myocardium from ischemia/reperfusion associated injury. Crit Care. 2003;7(6):R176-83.
30. Yalcin AA, Topuz M, Biyik I, Akturk IF, Celik O, Isıksacan N, et al. Role of insulin-like growth factor 1 in stent thrombosis under effective dual antiplatelet therapy. Postepy Kardiol Interwencyjnej. 2014;10(4):242-9.
31. Burchardt P, Gozdzicka-Jozefiak A, Zurawski J, Nowak W, Durzynska J, Link R, et al. Are elevated levels of IGF-1 caused by coronary arteriesoclerosis?: Molecular and clinical analysis. Protein J. 2010;29(8):538-44.
32. Vaessen N, Heutink P, Janssen JA, Witteman JC, Testers L, Hofman A, et al. A polymorphism in the gene for IGF-I functional properties and risk for type 2 diabetes and myocardial infarction. Diabetes. 2001;50(3):637-42.
33. Li Q, Li B, Wang X, Leri A, Jana KP, Liu Y, et al. Overexpression of insulin-like growth factor-1 in mice protects from myocyte death after infarction, attenuating ventricular dilation, wall stress, and cardiac hypertrophy. J Clin Invest. 1997;100(8):1991-9.
34. Konev AA, Smolyanova TI, Kharitonov AV, Serebryanaya DV, Kozlovsky SV, Kara AN, et al. Characterization of endogenously circulating IGFBP-4 fragments—Novel biomarkers for cardiac risk assessment. Clin Biochem. 2015;48(12):774-80.
35. Hjortebjerg R, Lindberg S, Hoffmann S, Jensen JS, Oxvig C, Bjerre M, et al. PAPP-A and IGFBP-4 fragment levels in patients with ST-elevation myocardial infarction treated with heparin and PCI. Clin Biochem. 2015;48(4-5):322-8.
36. Shehata M. Pregnancy-Associated Plasma Protein-A Levels and Coronary Angiographic Features in Acute Coronary Syndrome Patients. J Angiol. 2014;2014:420937.

37. Bonaca MP, Scirica BM, Sabatine MS, Jarolim P, Murphy SA, Chamberlin JS, et al. Prospective evaluation of pregnancy-associated plasma protein-a and outcomes in patients with acute coronary syndromes. J Am Coll Cardiol. 2012;60(4):332-8.
38. Gururajan P, Gurumurthy P, Nayar P, Rao GSN, Babu RS, Sarasabharati A, et al. Pregnancy associated plasma protein-A (PAPP-A) as an early marker for the diagnosis of acute coronary syndrome. Indian Heart J. 2012;64(2):141-5.
39. Laterza OF, Cameron SJ, Chappell D, Sokoll LJ, Green GB. Evaluation of pregnancy-associated plasma protein A as a prognostic indicator in acute coronary syndrome patients. Clin Chim Acta. 2004;348(1-2):163-9.