რეზიუმე

ინსულინური პომპით მკურნალობის როლი შაქრიანი დიაბეტი ტიპი2-ის მკურნალობაში (მიმოხილვითი სტატია)

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ლიტერატურის მიმოხილვაში მოტანილია მონაცემები მუდმივი კანქვეშა ინსულინური ინფუზიის, ანუ ინსულინური პომპით თერაპიის გავლენის შესახებ შაქრიანი დიაბეტის მქონე პაციენტებზე. სტატია მოიცავს შაქრიანი დიბეტის ეპიდემიოლოგიას, მონაცემებს ინსულინური პომპით თერაპიის გავლენის შესახებ კოგნიტიურ ფუნქციებსა და მეტაბოლურ პარამეტრებზე შაქრიანი დიაბეტის მქონე პაციენტებში. შესწავლილია 132 წყარო, მათგან 39 უახლესი სრული კვლევა და მეტაანალიზია. არ არის გამოყენებული 10 წელზე მეტი ხნის წყაროები და თეზისები. ნაჩვენებია ინსულინური პომპის უპირატესობანი და ნაკლოვანებები. სხვადასხვა წყაროში ერთხმად მიუთითებენ გლიკოზირებული ჰემოგლობინის გაუმჯობესების შესახებ მუდმივი კანქვეშა ინსულინური ინფუზიის შემდგომ. შედარებულია ეს უკანასკნელი და ინსულინის ყოველდღიური მრავალჯერადი ინიექცია. ლიტერატურის მიმოხილვა მოიცავს Pub Med-, Science Direct-, Springer- და Google-Scholar-ის ელექტრონული ბაზების 10-წლიანი პერიოდის მონაცემებს შაქრიანი დიაბეტის სხვადასხვა მეთოდით მკურნალობის შესახებ.

INSULIN-LIKE GROWTH FACTOR-1 AND ENDOSTATIN IN PATIENTS WITH MYOCARDIAL INFARCTION DEPENDING ON THE PRESENCE OF OBESITY

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Myocardial infarction (MI) leads to complex changes in the structure of the damaged and intact myocardium. Dilation of the left ventricle and thinning of the damaged tissue are the most significant structural changes that increase the risk of further complications. One of the leading mechanisms in the healing process in MI is the change of tissue metabolism and intensity of angiogenesis, resulting in left ventricular myocardial remodeling.

Obesity is the important comorbidity in cardiovascular diseases [1]. Unfortunately, there are only limited treatment options for improvement of metabolic status and prevention of cardiovascular events in comorbid pathology [2].

Regulators of metabolic processes with direct effect on various tissues and organs include insulin-like growth factor-1 (IGF-1), a peptide hormone that resembles insulin by structure and actively participates in anabolic reactions in connective tissue, muscles and heart. The main amount of IGF-1 is synthesized by the liver cells, but there are other types of cells that are also capable of producing IGF-1, in particular cardiomyocytes and endotheliocytes. The number of receptors for IGF-1 in the vascular endothelium is even greater than that for insulin receptors.

Unlike insulin, which is not produced in the tissues of the cardiovascular system, the local secretion of IGF-1 occurs through autocrine or paracrine mechanisms. In vitro studies administration of IGF-1 to transgenic mice caused proliferation of smooth muscle cells and inhibition of apoptosis that lead to the stabilization of atherosclerotic plaque. There is evidence that IGF-1 reduces the proliferation of smooth muscle cells in the intact endothelium, but stimulates in the damaged ones. IGF-1 is known to participate in the synthesis of nitrogen monoxide (NO) in endothelial cells, causing additional vasodilation of the arteries. Thus, it seems likely that many atherosclerotic and proliferative changes in arteries occur through “mediation” by IGF -1.

It is known that prolonged hypersecretion of IGF-1, which is observed in patients with acromegaly, underlies the formation of concentric hypertrophy of the myocardium and of an increase of the total mass of the heart [3]. According to Laplace’s law, the contractile possibilities of the cardiac muscle gradually decrease and the dilatation of all chambers of the heart develops, which also inevitably leads to heart failure. In addition, patients with hypersecretion of IGF-1 are 4-5 times more likely to develop hypertension and dyslipidemia in comparison with the general population, that accelerates the development of cardiovascular diseases.

Pilot studies have shown that the administration of exogenous IGF-1 to patients with severe heart failure (including patients with dilated cardiomyopathy) may improve structural changes in the myocardium and reduce the functional class of heart failure [4]. Resistance to IGF-1 is reported to be associated with a change of the thickness of the intima-media complex of the vascular wall in obesity [5].

People with cardiac ischemia, overweight and obesity of the I-II degrees have a lower risk of both general and cardiovascular mortality in comparison with normal and low weight persons [6]. Whether IGF-1 plays a protective role in the heart in these patients is not known yet.

The endogenous angiogenesis inhibitor, endostatin, was discovered in 1997 in the cultured media of hemangioblastoma cells [7]. Endostatin neutralization is known to promote angiogenesis in the myocardium, dramatically induce tissue fibrosis and remodeling, leading to worse outcomes. These results suggest that angiogenesis therapy may not be beneficial in the left ventricle (LV) remodelling after MI [8], nevertheless angiogenesis is believed to have a beneficial effect on LV remodeling after MI [9], therefore our study is necessary to reveal the effects of angiogenesis markers on LV remodelling.

The aim of the study - to study the markers of angiogenesis– IGF-1 and endostatin – in patients with acute MI according to the presence or absence of obesity.

Material and methods. The study involved 105 patients with acute MI and obesity who were treated in the infarctional department (mean age 64.6±7.4years). 55 of them had acute MI with obesity and 60 patients – acute MI without obesity. The groups studied were comparable by sex and age. The control group consisted of 20 healthy persons of corresponding age and sex.

MI was diagnosed according to the present guidelines (European Society of Cardiology (ESC) Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation, 2017).

Obesity was diagnosed according to American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for Comprehensive Medical Care of Patients With Obesity, 2016. Body mass index (BMI) was 18.5 to 24.9 kg/m^2 for normal weight and 30 kg/m^2 for obesity.

All patients underwent echocardiography with measurement of end-diastolic diameter (EDD), end-systolic diameter (ESD), end-systolic volume (ESV), end-diastolic volume (EDV), ejection fraction (EF). Echocardiography was performed by standard techniques with transducer (Siemens ACUSON X150).

ELISA was used for detection of the levels of troponin I (VEDALAB, France), total cholesterol (BIOCON, Germany), IGF-1 (MEDIAGNOST, Germany) and endostatin (BIOMEDICA, Austria).

Statistical processing was carried out using the program STATISTICA 7.0. Correlation analysis was performed by Spearman. Data are presented as M±m, where M – is mean and m – is standard error of mean. Significant differences were considered at $p < 0.05$.

Results and their discussion. Patients with MI showed increased levels of IGF-1 as compared to the control group ($p<0.05$) (Table 1).

Patients with MI and obesity also had significantly higher levels of IGF-1 as compared to the controls (180.64±12.2ng/ml, 114.3±7.2 ng/ml, accordingly).

The levels of IGF-1 in obese MI patients were statistically significantly higher than in the serum of non-obese patients with MI ($p<0.05$). Either obese or non-obese patients with MI showed higher endostatin levels than controls ($p<0.05$).

However, on the contrary to IGF-1 the levels of endostatin in the group of patients with MI and obesity were lower, than in the group of MI without obesity (148.26±6.04pmol/l and 169.83±8.39 pmol/l, accordingly, $p<0.05$).

Obese and non-obese patients with acute MI had higher levels of total cholesterol, triglycerides (TG), low-density lipoproteins (LDL), very-low-density lipoproteins (VLDL), atherogenic coefficient (AC) and lower levels of high-density lipoproteins (HDL) as compared to controls ($p<0.05$). Comparison of lipid profile parameters in acute MI patients with obesity showed significant differencies in triglycerides ($p<0.05$).

Correlation analysis in the group of the persons with MI and obesity revealed a presence of positive association between BMI and IGF-1 ($r=0.21$, $p<0.05$). Both in patients with MI and obesity and without obesity BMI correlated with endostatin ($r=0.22$, $r=0.2$, $p<0.05$) (Table 2, 3).

Table 1. Parameters of metabolism and angiogenesis in MI and concomitant obesity

Parameter	Patients with MI and obesity (n=22)	Patients with MI (n=24)	Controls (n=20)
IGF-1, ng/ml	180.64±12.2 #*	128.76±8.1 *	114.3±7.2
Endostatin, pmol/l	148.26±6.04 #*	169.83±8.39 *	130.05±7.3
Troponin I, mmol/l	4.67±0.74 #*	4.0±0.95*	0.09
Total cholesterol, mmol/l	5.18±0.18 *	5.05±0.25 *	4.4±0.15
HDL, mmol/l	1.17±0.03 *	1.12±0.04 *	1.37±0.03
Triglycerides, mmol/l	2.04±0.06 #*	1.7±0.11 *	0.56±0.01
LDL, mmol/l	3.12±0.2 *	3.02± 0.21 *	2.18±0.14
VLDL, mmol/l	0.86±0.03 *	0.81±0.06 *	0.28±0.01
Atherogeniccoefficient	3.63±0.21 *	3.42±0.24 *	2.42±0.11

*note: * – p<0.05 as compared to controls, # – p<0.05 as compared to patients with MI, HDL – high-density lipoproteins, LDL – low-density lipoproteins, VLDL – very-low-density lipoproteins*

Table 2. Correlation between the parameters of echocardiography and biochemical data for patients with myocardial infarction comorbidant obesity

Parameter	IGF-1	Endostatin	Troponin I	Total cholesterol
Troponin I	0,36*	0,06	–	-0.02
Total cholesterol	-0.23*	0.01	-0.02	–
EDD	-0.21*	0.24*	0.13	0.07
ESD	-0.22*	0.35*	0.11	0.03
ESV	-0.24*	0.25*	0.1	-0.04
EDV	-0.25*	0.27*	0.12	0.02
EF	0.1	0.03	0.03	0.12
Interventricular septum thickness	0.44*	-0.08	0.18	0.01
BMI	0.21*	0.22*	0.01	0.22*

*note: * – p<0.05*

Table 3. Correlation between the parameters of echocardiography and biochemical data for patients with myocardial infarction without obesity

Parameter	IGF-1	Endostatin	Troponin I	Total cholesterol
Troponin I	0,35*	-0,19	–	-0.12
Total cholesterol	-0.24*	0.15	-0.12	–
EDD	-0.21*	0.38*	0.13	0.14
ESD	-0.24*	0.4*	0.11	0.05
ESV	-0.37*	0.28*	0.05	0.09
EDV	-0.29*	0.28*	0.13	0.17
EF	0.45*	-0.15	-0.27	0.08
Interventricular septum thickness	0.52*	0.13	0.23	0.03
BMI	0.14*	0.2*	-0.29	0.08*

*note: * – $p<0.05$*

In patients with MI and obesity we observed negative correlation between IGF-1 and cardiohaemodynamic parameters: EDD ($r=-0.21$, $p<0.05$), ESD ($r=-0.22$, $p<0.05$), ESV ($r=-0.24$, $p<0.05$), EDV ($r=-0.25$, $p<0.05$) and positive correlations between IGF-1 and troponin I ($r=0.36$, $p<0.05$) and interventricular septum thickness ($r=0.44$, $p<0.05$).

On the contrary to IGF-1 endostatin showed positive correlations with cardiohaemodynamic parameters: EDD ($r=0.24$, $p<0.05$), ESD ($r=0.35$, $p<0.05$), ESV ($r=0.25$, $p<0.05$), EDV ($r=0.27$, $p<0.05$), endostatin whereas in patients with MI correlated stronger with EDD, ESD, ESV and EDV ($r=0.38$, $r=0.4$, $r=0.28$, $r=0.28$, $p<0.05$). Total cholesterol positively correlated with BMI ($r=0.22$, $p<0.05$) in patients with MI and obesity and did not correlate in patients without obesity.

Increased risk of cardiovascular events is observed both in excess and deficiency of IGF-1. The number of studies have shown a positive relationship between IGF -1 and atherosclerosis. On the other hand, a low level of IGF-1 is a predictor of MI and mortality, confirming the positive effects of IGF-1 – anti-apoptotic, antioxidative and stabilizing of atherosclerotic plaque, though in large prospective cohort studies these data were not confirmed [2].

In the present study levels of IGF-1 in MI and obesity were more increased as compared to the patients with MI. Similar findings have been found in other studies [10], that suggest the role of IGF-1 in atherogenesis in the intima of the vessels in MI and obesity.

Our study also demonstrated a relationship between BMI and IGF-1. These data did not contradict results of Jessica M. Faupel-Badger [11].The increase of IGF-1 was positively associated with the severity of dyslipidemia. The obtained results testify to involvement of IGF-1 in the pathogenesis of atherosclerosis.

Patients with MI and obesity showed lower levels of endostatin as compared to non-obese. Thus, obesity leads to decrease of angiogenesis inhibitor factor activity and activation of angiogenesis promoter.

The obtained correlations indicate the relationship between serum changes of endostatin and IGF-1 and remodeling of the left ventricular myocardium, confirming the notion, that IGF-1 is involved in hypertrophy of myocardium, that is also demonstrated by other investigations [12].

Conclusions.

Our findings demonstrate that patients with acute MI have increased IGF-1 and endostatin in comparison with the controls. The presence of obesity is accompanied by an increase of angiogenesis activator IGF-1 and decrease of angiogenesis inhibitor endostatin.

High activity of IGF-1 is accompanied by increase of proatherogenic lipids and thickening of the wall of the left ventricle in patients with MI and obesity, whereas hyperendostatinemia is associated with left ventricle dilation.

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SUMMARY

INSULIN-LIKE GROWTH FACTOR-1 AND ENDOSTATIN IN PATIENTS WITH MYOCARDIAL INFARCTION DEPENDING ON THE PRESENCE OF OBESITY

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Aim of the study - to study the markers of angiogenesis–IGF-1 and endostatin – in patients with acute myocardial infarction according to the presence or absence of obesity.

The study involved 105 patients with acute myocardial infarction (MI) with concomitant obesity who were treated in the infarctional department (mean age 64.6±7.4 years), 55 of them – with acute MI with comorbidant obesity and 60 patients – with acute MI without obesity. The groups were comparable by sex and age. The control group consisted of 20 healthy persons of corresponding age and sex.

In obese and non-obese patients with MI the levels of IGF-1 were statistically significantly higher than those of persons in the control group ($p<0.05$). The levels of IGF-1 in acute MI with obesity were statistically significantly higher than in the serum of patients with MI without obesity (180.64±12.2 ng/ml and 128.76±8.1 ng/ml, accordingly, $p<0.05$).

Patients with acute MI showed increased IGF-1 and endostatin in comparison with the controls. The presence of obesity in MI was accompanied by an increased IGF-1 and decreased endostatin as compared to patients with MI.

In patients with MI and obesity, high activity of IGF-1 was accompanied by high levels of proaterogenic lipids with reduced volumes and thickening of the interventricular wall of the left ventricle. Unlike IGF-1 hyperendostatinemia was associated with left ventricle dilation.

Keywords: endostatin, insulin-like growth factor-1, myocardial infarction, obesity.

РЕЗЮМЕ

ИНСУЛИНОПОДОБНЫЙ ФАКТОР РОСТА-1 И ЭНДОСТАТИН У ПАЦИЕНТОВ С ОСТРЫМ ИНФАРКТОМ МИОКАРДА В ЗАВИСИМОСТИ ОТ НАЛИЧИЯ ОЖИРЕНИЯ

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Целью исследования явилось изучить маркеры ангиогенеза – инсулиноподобный фактор роста-1 и эндостатин, у пациентов с острым инфарктом миокарда в зависимости от наличия или отсутствия ожирения.

В исследовании приняли участие 105 пациентов с острым инфарктом миокарда (ИМ) с сопутствующим ожирением, которые лечились в инфарктном отделе (средний возраст 64,6±7,4 года), 55 из них с острым ИМ и сопутствующим ожирением и 60 пациентов с острым ИМ без ожирения. Контрольная группа состояла из 20 здоровых лиц соответствующего возраста и пола.

Установлено, что у пациентов с ИМ с ожирением и без ожирения уровни инсулиноподобного фактора роста-1 (ИФР-1) и эндостатина были выше, чем у лиц контрольной группы ($p<0,05$). Уровень ИФР-1 при остром ИМ с ожирением был статистически достоверно выше, чем в сыворотке пациентов с ИМ без ожирения (180,64±12,2 нг/мл и 128,76±8,1 нг/мл, соответственно, $p<0,05$).

У больных ИМ и ожирением были увеличены показатели ИФР-1 и уменьшены показатели эндостатина в сравнении с больными острым ИМ без ожирения.

Выявлено, что у пациентов с ИМ и ожирением повышение активности ИФР-1 сопровождалось высоким уровнем проатерогенных липидов, уменьшенными объемами полостей сердца и утолщением межжелудочковой стенки левого желудочка. Гиперэндостатинемия ассоциировалась с дилатацией левого желудочка.

რეზიუმე

ინსულინის მსგავსი ზრდის ფაქტორი-1 და ენდოსტატინი მიოკარდიუმის მწვავე ინფარქტით პაციენტებში სიმსუქნეზე დამოკიდებულებით

დ. მარტოვიცკი, პ. კრავჩუნი, ა. შელესტი

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კვლევის მიზანს წარმოადგენდა ანგიოგენეზის მარკერების – ინსულინის მსგავსი ზრდის ფაქტორ-1–ის და ენდოსტატინის შესწავლა მიოკარდიუმის მწვავე ინფარქტით პაციენტებში სიმსუქნის არსებობა/არარსებობაზე დამოკიდებულებით.

კვლევაში ჩართული იყო მიოკარდიუმის მწვავე ინფარქტით (მმი) 105 პაციენტი თანამდევი სიმსუქნით, საშუალო ასაკი – 64,6±7,4 წელი, მათ შორის 55 - მწვავე ინფარქტით და სიმსუქნით, 60 – მწვავე ინფარქტით სიმსუქნის გარეშე. საკონტროლო ჯგუფი შეადგინა შესაბამისი ასაკისა და სქესის 20 ჯანმრთელმა პირმა.

დადგინდა, რომ მმი-თ პაციენტებში სიმსუქნით და სიმსუქნის გარეშე ინსულინის მსგავსი ზრდის ფაქტორ-1–ის (იზფ) და ენდოსტატინის დონე უფრო მაღალია, ვიდრე საკონტროლო ჯგუფში ($p<0,05$). იზფ-1-ის დონე მმი-ით და სიმსუქნით პაციენტებში სტატისტიკურად სარწმუნოდ მეტია, ვიდრე სიმსუქნის არმქონე პაციენტებში (180,64±12,2 ნგ/მლ, 128,76±8,1 ნგ/მლ, შესაბამისად, $p<0,05$). მმი-ით და სიმსუქნით პაციენტებში მომატებულია იზფ-1-ის მაჩვენებლები და შემცირებულია ენდოსტატინის მაჩვენებლები, მმი-ით და სიმსუქნის გარეშე პაციენტებთან შედარებით.

დადგენილია, რომ პაციენტებში მმი-ით და სიმსუქნით იზფ-1-ის მაღალ აქტივობას თან ახლავს პროატეროგენული ლიპიდების დონის ზრდა, გულის ღრუების მოცულობათა შემცირება და მარცხენა პარკუჭის პარკუჭთაშუა ძგიდის გასქელება. ამასთან, ჰიპერენდოსტატინემია ასოცირებულია მარცხენა პარკუჭის დილატაციასთან.