UDC: 616.12-005.4-06-06:616.36-003.8]-092 DOI: 10.14739/2310-1210.2016.5.82568

N. S. Mykhailovska, L. Ye. Miniailenko

The peculiarities of adiponectin and resistin interrelationships with the components of metabolic syndrome in patients with coronary heart disease and concomitant nonalcoholic fatty liver disease

Zaporizhzhia State Medical University, Ukraine

Key words: *Coronary Artery Disease, Non-Alcoholic Fatty Liver Disease, Adiponectin, Resistin, Metabolic Syndrome.*

Objective. To investigate the interrelationships between adiponectin and resistin levels with the components of metabolic syndrome in patients with coronary heart disease and concomitant nonalcoholic fatty liver disease.

Methods. Cross-cohort analytical study involved 46 patients, the primarily selected group consisted of 24 patients, mean age 58 y (44.64) with documented coronary artery disease, stable exertional angina of II–III functional class combined with NAFLD; comparison selected group: 20 patients, mean age was 60.5 y (50.5; 65) with coronary artery disease without NAFLD. The control selected group consisted of 12 healthy individuals.

Results. A significant increase in the value of BMI by 13 % ($p<0.05$), triglyceride levels by 36 % ($p<0.05$) were observed in patients with coronary artery disease and NAFLD, there was valid ($p<0.05$) increase in insulin levels compared to healthy individuals (4.75 times) and CHD patients without structural and functional changes in the liver (in 2.42 times). HOMA index levels were 5 times higher in comparison to healthy people and 2.35 times higher compared to patients with CHD ($p<0.05$). The adiponectin serum level in patients with coronary heart disease and NAFLD was 60 % lower than among healthy individuals ($p<0.05$), and 31.6 % ($p<0.05$) than in the comparison group, while the level of resistin was 48 % higher in patients of the primarily selected group compared to the control selected group, and 27 % higher than in the comparison selected group ($p<0.05$).

Conclusions. Patients with CHD associated with the nonalcoholic fatty liver disease are characterized by adipocytokine imbalance: the reduction of the adiponectin concentration and the elevation of the resistin levels if compared to the control selected group and CHD patients without liver disease. In patients with CHD combined with NAFLD, were determined multi-directional correlative interrelationships of adiponectin and resistin with components of metabolic syndrome, thus indicating pathogenesis links of found violations.

Zaporozhye medical journal 2016; №5 (98): 25–30

Особливості взаємозв'язків адипонектину та резистину з компонентами метаболічного синдрому у хворих на ішемічну хворобу серця із супутньою неалкогольною жировою хворобою печінки

Н. С. Михайловська, Л. Є. Миняйленко

Мета роботи – вивчення взаємозв'язку між рівнями адипонектину та резистину з компонентами метаболічного синдрому у хворих на ішемічну хворобу серця із супутньою неалкогольною жировою хворобою печінки.

Матеріали та методи. До поперечного когортного аналітичного дослідження в паралельних групах залучили 46 пацієнтів. Основну групу становили 24 хворих, медіана віку – 58 (44; 64) з документально підтвердженою ІХС: стабільною стенокардією напруження II–III функціонального класу (ФК) у поєднанні з НАЖХП; група порівняння – 20 хворих, середній вік – 60,5 (50,5; 65) з ІХС без НАЖХП. Контрольну групу становили 12 здорових осіб.

Результати. У пацієнтів з ішемічною хворобою серця та НАЖХП спостерігали вірогідне збільшення ІМТ на 13 % ($p<0,05$), рівня тригліцериду – на 36 % ($p<0,05$) порівняно з хворими без патології печінки, рівня інсуліну – в 4,75 раза порівняно зі здоровими особами ($p<0,05$) і в 2,42 раза порівняно з хворими на ІХС без структурно-функціональних змін у печінці ($p<0,05$). Рівень індексу HOMA був уп'ятеро вищим порівняно зі здоровими людьми ($p<0,05$) та у 2,35 раза вищим порівняно з пацієнтами з ІХС ($p<0,05$). Рівень сироваткового адипонектину в пацієнтів з ішемічною хворобою серця та НАЖХП був на 60 % нижчим, ніж у здорових осіб ($p<0,05$), і 31,6 %, ніж у групі порівняння ($p<0,05$), водночас рівень резистину був на 48 % вищим у хворих основної групи порівняно з контрольною групою ($p<0,05$) і на 27 % вищим, ніж у групі порівняння ($p <0,05$).

Висновки. Хворим на ІХС, асоційовану з неалкогольною жировою хворобою печінки, притаманний дисбаланс адипоцитокінів: зменшення концентрації адипонектину та збільшення рівня резистину порівняно з контрольною групою та з хворими на ІХС без патології печінки. У хворих на ішемічну хворобу серця, що поєднана з неалкогольною жировою хворобою печінки, встановлені різноспрямовані кореляційні взаємозв'язки адипонектину та резистину з компонентами метаболічного синдрому, що свідчить про патогенетичний зв'язок виявлених порушень.

Ключові слова: *ішемічна хвороба серця, неалкогольна жирова хвороба печінки, адипонектин, резистин, метаболічний синдром.*

Запорізький медичний журнал. – 2016. – №5 (98). – С. 25–30

Особенности взаимосвязи адипонектина и резистина с компонентами метаболического синдрома у больных ИБС и сопутствующей неалкогольной жировой болезнью печени

Н. С. Михайловская, Л. Е. Миняйленко

Цель работы – изучение взаимосвязи между уровнями адипонектина и резистина с компонентами метаболического синдрома у больных ишемической болезнью сердца с сопутствующей неалкогольной жировой болезнью печени.

Материалы и методы. К поперечному когортному аналитическому исследованию в параллельных группах привлечено 46 пациентов. Основную группу составили 24 больных, медиана возраста – 58 (44; 64) с документально подтверждённой ИБС: стабильной стенокардией напряжения II–III функционального класса (ФК) в сочетании с НАЖБП; в группу сравнения вошло 20 больных, средний возраст – 60,5 (50,5; 65), с ИБС без НАЖБП. Контрольную группу составили 12 здоровых лиц.

Результаты. У пациентов с ишемической болезнью сердца и НАЖБП наблюдались достоверное увеличение ИМТ на 13 % ($p<0,05$), уровня триглицеридов на – 36 % ($p<0,05$) по сравнению с больными без патологии печени, уровня инсулина – в 4,75 раза по сравнению

со здоровыми лицами (p<0,05) и в 2,42 раза по сравнению с больными ИБС без структурно-функциональных изменений в печени (p<0,05). Уровень индекса HOMA был в 5 раз выше по сравнению со здоровыми лицами (p<0,05) и в 2,35 раза выше по сравнению с пациентами с ИБС (p<0,05). Уровень сывороточного адипонектина у пациентов с ишемической болезнью сердца и НАЖБП был на 60 % ниже, чем у здоровых лиц (p<0,05), и 31,6 %, чем в группе сравнения (p<0,05), в то время как уровень резистина был на 48 % выше у больных основной группы по сравнению с контрольной группой (p<0,05) и на 27 % выше, чем в группе сравнения (p<0,05).

Выводы. Больным ИБС, ассоциированной с неалкогольной жировой болезнью печени присущ дисбаланс адипоцитокинов: уменьшение концентрации адипонектина и увеличение уровня резистина по сравнению с контрольной группой и с больными ИБС без патологии печени. У больных ишемической болезнью сердца, коморбидной с неалкогольной жировой болезнью печени, установлены разнонаправленные корреляционные взаимосвязи адипонектина и резистина с компонентами метаболического синдрома, что свидетельствует о патогенетической связи выявленных нарушений.

Ключевые слова: *ишемическая болезнь сердца, неалкогольная жировая болезнь печени, адипонектин, резистин, метаболический синдром.*

Запорожский медицинский журнал. – 2016. – №5 (98). – С. 25–30

Introduction: coronary heart disease (CHD) is one of the most significant health and social problems in Ukraine and worldwide [1]. The abdominal type of obesity is one of the major reasons of metabolic disorders and independent risk factor for coronary heart disease development [2]. According to the Framingham Heart Study, the obesity reduces life expectancy by 6–7 years. The prevalence of coronary heart disease among men and women with obesity is 2.5 times higher than among people with normal body weight [3].

In recent years, more attention is paid to the study of the adipose tissue state because of the increased rate of comorbid and polimorbid diseases. It is proved that the adipose tissue is not only the excess of neutral fat but also one of the largest endocrine glands that produces about 10 different hormones (adipocytokines) and interacts with almost all body organs and systems. However, the interrelationships between adipocytokines and the development of coronary heart disease and comorbidities are studied insufficiently [4].

One of the diseases concomitant to the obesity is a nonalcoholic fatty liver disease (NAFLD) that occurs as hepatic steatosis and nonalcoholic steatohepatitis (NASH) [5]. According to the latest statistics, the NAFLD prevalence in Western Europe is 20–30 %, in Asia – 15 %, Russia – 27 %, including cirrhosis found in 3 % of patients with steatosis – 79.9 %, steatohepatitis – 17.1 % [6].

The statistical data on the prevalence of this disease in Ukraine are absent because of the asymptomatic disease course on the early and late stages; hence this complicates the diagnostics [7]. NAFLD is regarded as a condition associated with insulin resistance (IR), regardless of weight, body mass index (BMI), fat distribution and glucose tolerance [8].

In the development of IR, the important role is played by adipocytokine proteohormones formed in adipose tissue. The main adipocytokines that enhance the effect of insulin are leptin and resistin, tumor necrosis factor – alpha (TNF-a), interleukin-6, however, adiponectin contributes to insulin resistance [9].

Two of the adipocytokines playing a direct role in the remodeling of the myocardium are adiponectin and resistin. It was established that low adiponectin concentration in blood serum is associated with the increased risk of cardiovascular pathology; it is confirmed primarily in patients with NAFLD [10]. On the other hand, the low adiponectin concentration in blood serum is closely related to the high fat content in the liver, and with reduced metabolism of lipoproteins that contain large amounts of triglycerides. This low concentration may also influence the predisposition of coronary vessels towards the formation of atheromas, thus influencing sufficiently the pathogenesis of acute coronary syndrome. Under this circumstance, the high level of adiponectin is associated with congestive heart failure and mortality caused by it [11]. The adiponectin inhibits the expression of vascular cell adhesion molecules (vascular cell adhesion molecule – VCAM-1) by the E-selectine endotheliocytes, and the intercellular adhesion molecules (intercellular adhesion molecule – ICAM-1). Thus, the lack of adiponectin, which has the effect of vessels protection, negatively impacts the processes of atherogenesis [12].

At present, among all adipocytokines, big value is given to the study of the metabolic impact of resistin as a pathogenic factor in the development of obesity and insulin resistance. This adipocytokine is regarded as «intrahepatic cytokine» that affects the function and stimulates the anti-inflammatory effect in stellate cells of the liver, the key fibrosis modulators [13].

The anti-inflammatory effect of resistin on atherosclerosis confirms its participation in the development of endothelial dysfunction through the induction of endothelin-1secretion. In the Italian Gtargano Heart Study (2013) the independent predictor role of resistin to increase mortality from all causes was discovered [14], in addition, it was found out that the elevation of resistin levels in blood plasma is associated with the increased risk of 5-year cardiovascular mortality. The mechanisms underlying the identified violations had not been yet clarified [15].

Today, a perspective and promising are studying of the clinical and pathogenetic significance of resistin and adiponectin in patients with nonalcoholic fatty liver disease combined with coronary artery disease, and the interrelationships of these substances with the components of metabolic syndrome.

Objective

To investigate the interrelationships between adiponectin and resistin levels with the components of metabolic syndrome in patients with coronary heart disease and concomitant nonalcoholic fatty liver disease.

Materials and methods

The study was conducted in the Zaporizhzhia Central Clinical Hospital № 4, which is the clinical base of the Zaporizhzhia State Medical University Department of General Practice – Family Medicine.

Cross-cohort analytical study in parallel groups involved 46 patients, the primary selected group consisted of 24 patients, mean age 58 y (44, 64) with documented coronary artery disease, stable exertional angina of II–III functional class (FC) combined

with NAFLD; comparison selected group: 20 patients, mean age was 60.5 y (50.5; 65) with coronary artery disease without NAFLD. The control selected group consisted of 12 healthy individuals. Groups were comparable in age, sex, comorbidities nature, duration of CHD.

Exertional angina of FC II and III was diagnosed under the classification of the Canadian Heart Association. The presence of morphological and functional features of nonalcoholic fatty liver disease was determined with ultrasound examination of the liver, by the defining of its structure, size, thickness of its parts, density, ultrasound conduction, the state of the bile ducts and vascular pattern. NAFLD is diagnosed according to the following criteria: increased liver mass, increased echogenicity, reduced ultrasound conduction, reduced visualization of portal and hepatic veins branches.

Criteria for the patient to be included into the study were the next: informed consent of the patient, the presence of documented (verified) CHD and NAFLD. The patient could be excluded from the study under the following criteria: if he/she suffers alcoholic liver disease or cirrhosis, autoimmune and viral hepatitis; decompensated heart failure; acute coronary syndrome or acute cerebrovascular accident in less than 3 months prior to the study; congenital or acquired heart defects; cancer; autoimmune disorders.

In our work we followed the principles of bioethics: the main provisions of the European Convention on Human Rights and Biomedicine (from 04.04.1997), GCP (1996), Helsinki Declaration of the World Medical Association on ethical principles of scientific medical research involving human beings (1964–2000) and MOH of Ukraine № 281 of 01.11.2000. The study protocol was approved by the Ethics Committee of the Zaporizhzhia State Medical University, Ukraine. Before being included in the study, all participants provided written consent.

On the admission to the hospital all patients with coronary artery disease were subjected to a comprehensive examination under the generally accepted standards (MOH Ukraine № 436 of 03.07.2006). Anthropometric measurements included the definition of height, weight, body mass index: BMI = body weight (kg)/height (m²). The assessment of total cholesterol level, triglycerides (TG), high-density lipoproteins (HDL) were performed with Biolatest assay kit (Czech Republic) by using automatic biochemical photometer-analyzer. The level of low-density lipoproteins (LDL) was calculated with the Friedewald formula (1972): LDL-C = Total cholesterol – (HDL cholesterol + TG/2.2). The atherogenic index (AI) was determined by the following formula: IA = (Total cholesterol – HDL cholesterol)/HDL cholesterol. To measure the degree of insulin resistance the index HOMA-IR was used, it is calculated on the basis of basal glucose (mmol/l) and basal insulin levels (mkED/ml) under the formula: (glucose × insulin)/22.5.

On the basis of Medical and Laboratory Training Center ZSMU (Director – M.D., Professor A. Abramov) with the help of standard ELISA reagent kits, the levels of insulin (Monobind, USA); adiponectin (Mediagnost, Germany), resistin (Mediagnost, Germany) were measured. All available reagents were used under the instructions for the analysis, added to the set.

Statistical data processing was carried out using the software package "Statistica 10.0". (StatSoft Inc., № AXXR712D833214-FAN5) according to generally accepted practice. Analysis of the nature of the distribution of variables was assessed under the Kolmogorov-Smirnov's criterion (D). Since all the analyzed data differed from a normal distribution, we used Mann-Whitney U-criterion to compare indexes from two independent samples. Assessment of the interrelationship between pairs of independent indexes, expressed in quantitative scale, was carried out due to the Spearman rank correlation coefficient (r). The assessment of the correlation coefficients probability was performed by comparing the calculated coefficients to the critical ones. All data are presented as median and distribution quartiles, Me (Q25; Q75). Differences were considered significant at $p<0.05$.

Results

The expressiveness of the metabolic syndrome components depending on the NAFLD presence in patients with coronary artery disease is presented in *Table 1*.

Table 1

Expressiveness of metabolic syndrome components depending on the NAFLD presence in patients with coronary artery disease

Index, Unit (of measurement)	Control selected group (n=12)	CHD and NAFLD (n=15)	CHD (n=13)
BMI, kg/m²	26.29 (24.08; 29.26)	32.44 (29.13; 37.62)*#	28.73 (27.7; 31.88)
Waist, sm	80.66 (73.94; 96.42)#	94.82 (88.5; 105.1)*#	89.13 (79.3; 101.6)
Systolic BP	125.0 (110.0; 130.0)	160.0 (160.0; 170.0)*#	140.0 (130.0; 145.0)
Dyastolic BP	80.0 (70.0; 90.0)	95.0 (90.0; 100.0)	80.0 (65.0; 90.0)
General cholesterol, mmol/l	4.84 (4.57; 6.32)	5.67 (4.24; 6.29)	5.01 (4.21; 5.55)
LDL, mmol/l	2.86 (2.14; 4.29)	3.20 (2.79; 3.57)	3.91 (3.35; 4.1)
HDL, mmol/l	1.2 (1.12; 1.48)	0.96 (0.86; 1,34)	1.11 (0.75; 1.37)
TG, mmol/l	1.06 (1.05; 1.13)	2.27 (1.28; 2.75)*#	1.66 (0.8; 1.95)
Atherogenicity index	2.45 (2.05; 3.19)	3.63 (3.42; 3.81)	3.03 (2.13; 3.76)
Insulin, mkOd/ml	3.57 (3.43; 5.33)	17.00 (6.33; 22.77)*#	7.41 (0.57; 13.50)
Glucose, mmol/l	4.20 (4.1; 4.72)	5.00 (4.10; 5.80)	4.35 (3.90; 4.90)
HOMA-IR	0.66 (0.62; 0.99)	3.37 (1.50; 5.80)*#	1.43 (0.68; 1.73)

Notes: * – the probability of indexes difference if compared to the control selected group ($p<0.05$); # – the probability of indexes difference if compared to the patients with coronary artery disease ($p<0.05$).

In patients with coronary artery disease and NAFLD, a significant increase in the value of BMI was observed compared to the patients with coronary heart disease by 13 % and to 22.25 % correspondingly if compared to the control selected group ($p<0.05$).

The trend of increasing the total cholesterol and LDL cholesterol levels, atherogenic index and of reducing the HDL cholesterol in the primarily selected group compared to the patients with CHD and practically healthy individuals was observed. The triglyceride levels in patients with coronary artery disease and NAFLD was probably 2 times higher compared to the control selected group and 36 % – compared to the patients without liver disease pathologies ($p<0.05$).

While analyzing the insulin resistance indicators the following changes were estimated: the credible difference in the glucose level between selected groups was not observed. In patients with coronary heart disease associated with NAFLD, there was valid ($p<0.05$) increase in insulin levels compared to healthy individuals (4.75 times) and CHD patients without structural and functional changes in the liver (in 2.42 times). A similar tendency was observed regarding the HOMA index levels. It's 5 times increase in comparison to healthy people and 2.35 times increase compared to patients with CHD ($p<0.05$) were estimated.

Therefore, in patients with combined coronary heart disease and NAFLD, the presence of all components of metabolic syndrome is observed, the most pronounced are following: abdominal obesity, hypertriglyceridemia, and hypertension.

The levels of adiponectin and resistin in patients with coronary artery disease depending on the NAFLD availability are presented in *Table 2.*

The imbalance of adipocytokines level in patients with coronary artery disease with concomitant NAFLD was discovered (*Fig. 1*). The adiponectin serum level in patients with coronary heart disease and NAFLD was 60 % lower than among healthy individuals ($p<0.05$), and 31.6 % ($p<0.05$) lower than in the comparison selected group, while the level of resistin was 48 % higher than in patients of the primarily selected group compared to the control selected group, and 27 % higher than in the comparison selected group ($p<0.05$). Under this, patients with coronary artery disease without NAFLD did not differ substantially in the levels of adiponectin and resistin from healthy individuals.

The observed interrelationships between hormones of fat tissue and indexes of carbohydrate and lipid metabolism, anthropometric parameters, insulin resistance in patients with coronary heart disease associated with NAFLD (*Table 3*).

As it is shown in *Table 3*, adipocytokines demonstrate multi-directional correlative relations with the components of metabolic syndrome.

Hypoadiponectinemia is associated with the increased BMI, CT, CAT expressiveness of insulin resistance, proatherogenic blood changes, while the increase in resistin levels is related to opposite changes.

The obtained data coincide with the results of international and domestic scientists. Thus, Y. Arita et al. (2003) specified that adiponectin plasma concentrations negatively correlate with BMI. Prospective studies have shown that adiponectin levels decreased progressively with the development of obesity, and on the contrary, under the weight reduction, the increase of circulating adiponectin levels is observed [16]. Adiponectin is mostly associated with abdominal fat tissue redistribution. Thus, according to me. M. Cnop et al. (2003) the level of blood serum adiponectin negatively correlates with the volume of intra-abdominal adipose tissue [17].

At the same time, the strong correlative dependence of adiponectin level with insulin sensitivity index is shown, that may indicate the interrelationship of low adiponectin level

Table 2

The levels of adiponectin and resistin in patients with coronary artery disease depending on the NAFLD availability

Index, Unit (of measurement)	Control selected group (n=12)	CHD and NAFLD (n=15)	CHD (n=13)
Adiponectin, mkg/ml	14.74 (14.3; 15.6)	5.93 (2.91; 8.03)*#	8.67 (5.35; 10.27)
Resistin, ng/ml	6.32 (5.04;7.98)	9.39 (5.04; 15.12)*#	7.35 (6.93; 9.45)

Notes: * – the probability of indexes difference if compared to the control selected group ($p<0.05$); # – the probability of indexes difference if compared to the patients with coronary artery disease ($p<0.05$).

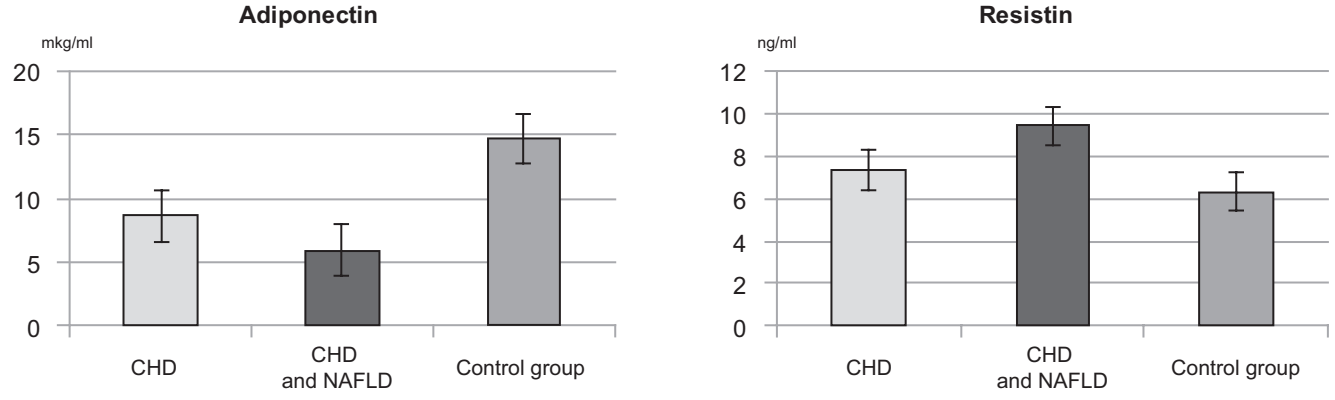

Fig. 1. The Concentration of adiponectin and resistin in patients with coronary heart disease, depending on the availability NAFLD.

Table 3

Correlative interrelationships between adiponectin and resistin and components of metabolic syndrome in patients with CHD associated with nonalcoholic fatty liver disease

Index	BMI	Waist	Systolic BP	Insulin	Glucose	HOMA	General cholesterol	TG	Atherogenicity index
Adiponectin	(r= -0.44; p<0.05)	(r= -0.68; p<0.05)	(r= -0.58; p<0.05)	(r= -0.47; p<0.05)	(r= -0.62; p<0.05)	(r= -0.42; p<0.05)	(r= -0.60; p<0.05)	(r= -0.55; p<0.05)	(r= -0.81; p<0.05)
Resistin	(r=+0.50; p<0.05)	(r=+0.63; p<0.05)	(r=+0.60; p<0.05)	(r=+0.42; p<0.05)	(r=+0.59; p<0.05)	(r= +0.35; p>0.05)	(r= +0.34; p>0.05)	(r=+0.42; p<0.05)	(r=+0.54; p<0.05)

with the development of insulin resistance [18]. According to S. A. Butrova et al. (2006), hypoadiponectinemia in men with abdominal obesity is associated with metabolic disorders, 42 % of patients were diagnosed hypertriglyceridemia 58 % – hypercholesterolemia and 52 % – insulin resistance. At low adiponectin level, the metabolic syndrome was diagnosed in 52 % of men with abdominal obesity [19]. In a number of studies, the clinical significance of hypoadiponectinemia as a risk factor for cardiovascular disease was evidenced. According to Y. Matsuzawa (2010), the low level of adiponectin is the independent risk factor for coronary heart disease and NAFLD [18]. According to the results of G. Musso and C. Finelli (2013), low levels of adiponectin in patients with NASH correlate to the development of the disease [20]. Clinical studies verified that NAFLD patients have reduced adiponectin level and it correlates oppositely with the severity of inflammation and liver damage [21]. It is proved that adiponectin reduces the degree of steatosis under the high-energy diet, obesity, and insulin resistance [22]. A. T. Teplyakov et al. (2015) suggested that the continuous running of resistin-induced inflammation plays a significant role in the development of insulin resistance [23].

Today, numerous studies that link the pathological role of obesity with elevated levels of circulating resistin are conducted. C. H. Sheng et al. (2013) elicited a positive correlative relationship between the degree of obesity, insulin resistance and increase in the levels of resistin [24]. However, it was discovered in the study of J.V. Silha et al. (2004) that resistin does not correlate with BMI, but its relationship with IP is significant. In their studies, E. Tsochatzis and C. Pagano (2009) showed that serum levels of resistin in patients with NAFLD are higher than in the control selected group, and positively correlate with inflammation and liver fibrosis severity [25].

Conclusions

1. In patients with coronary artery disease, combined with NAFLD the increased levels of triglycerides, systolic blood pressure, body mass index, waist circumference, HOMA index were determined compared to those of the control selected group and in patients with coronary artery disease without liver pathology.

2. Patients with CHD associated with the nonalcoholic fatty liver disease are characterized by adipocytokine imbalance: the reduction of the adiponectin concentration and the elevation of the resistin levels if compared to the control selected group and CHD patients without liver disease.

3. Multi-directional correlative interrelationships of adiponectin and resistin with components of metabolic syndrome were determined in patients with coronary heart disease combined with nonalcoholic fatty liver disease, thus indicating pathogenesis links of found violations.

Prospects for further research: the study of the interrelationships of hormones of adipose tissue with the clinical course of CHD associated with nonalcoholic fatty liver disease and the development of criteria for the selection of optimal treatment regimens of these patients is an important area for further research.

Conflicts of Interest: authors have no conflict of interest to declare.

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Information about authors:
Mykhailovska N. S., MD, PhD, DSci, Professor, Head of the Department of General Practice – Family Medicine, Zaporizhzhia State Medical University, Ukraine.
Miniailenko L. Ye., PhD student at the Department of General Practice – Family Medicine, Zaporizhzhia State Medical University, Ukraine, E-mail: luba89@gmail.com.
Відомості про авторів:
Михайловська Н. С., д-р мед. наук, професор, зав. каф. загальної практики – сімейної медицини, Запорізький державний медичний університет, Україна.
Міняйленко Л. Є., аспірант каф. загальної практики – сімейної медицини, Запорізький державний медичний університет, Україна, E-mail: luba89@gmail.com.
Сведения об авторах:
Михайловская Н. С., д-р мед. наук, профессор, зав. каф. общей практики – семейной медицины, Запорожский государственный медицинский университет, Украина.
Миняйленко Л. Е., аспирант каф. общей практики – семейной медицины, Запорожский государственный медицинский университет, Украина, E-mail: luba89@gmail.com.

Поступила в редакцию 28.09.2016 г.