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STUDY THE ROLE OF INTERCELLULAR MEDIATORS IN THE METABOLISM OF CONNECTED TISSUE IN CHILDREN WITH CARDIOMYOPATHY AND OSTEOPENY

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Abstract

Introduction. Undifferentiated forms of connective tissue dysplasy (UCTD) characterized by multiple organ changes and represent significant difficulties in diagnosis, prognosis assessment and correction capabilities. The most significant changes are manifestations UCTD musculoskeletal and cardiovascular system. However, to date, unclear mechanisms of cytokine regulation of metabolism CT, providing optimum intercellular interaction.

Objective - determine the profiles intercellular mediators and their significance in the development of common disorders scheme remediation regulation of connective tissue (CT) in children with cardiomyopathy and osteopeny.

Materials and Methods Investigated group consisted of 80 children with cardiomyopathy and osteopeny aged 8 to 14, boys - 42 Girls - 38 control group consisted of 30 healthy children of similar age. We investigated the content of RANKL, OPG, IL-1 RA, IL-17, TGF-1β, visfatyn and adiponectin in serum by enzyme immunoassay.

Results of the study established that the development of osteopeny associated with an imbalance in the system: ligand receptor activator of nuclear factor κβ (RANKL) / receptor activator of nuclear factor κβ (RANK) / osteoprotegerin (OPG), which leads to activation osteoklastoheneza and increased bone resorption. The content of RANKL and OPG children in the study group was significantly higher than in the control group (RANKL - 0.28 ± 0.02 pmol / l at a rate of 0.21 ± 0.02 pmol / L ($p < 0,05$); OPG 74.7 ± 3.62 pg / ml at a rate 62.9 ± 2.48 ($p < 0.05$)). There was a violation adypokinovoho exchange and reduced production of the cytokine IL-17,

which is a direct inducer fibroblasts. Average levels of IL-1 RA, IL-17 adiponectin and visfatyne significantly decreased and were: IL-1 RA - 169 ± 14.2 pg / ml at a rate of 264 ± 12.3 pg / ml ($p < 0.05$), IL-17 - 13.9 ± 0.43 pg / ml at a rate of 30.2 ± 1.26 ($p < 0.05$) Adiponectin - 18.3 ± 0.23 mg / ml at a rate of 20.9 ± 0.22 mg / ml ($p < 0.05$) visfatyn -158 ± 7.4 ng / ml at a rate of 158 ± 7.4 ng / ml ($p < 0.05$). Changes in the expression of TGF-1β was detected.

Conclusions. In children with cardiomyopathy and osteopeny in the background UCTD there is an imbalance in the system of regulation of the functional system of connective tissue (FSCT) at intercellular mediators who manifested the presence of pathological processes of biosynthesis deactivation CT. Identified changes may indicate a violation of a framework for the regulation of CTs remodeling and reduction of reserves of adaptation that should see the continued dynamic processes of remodeling and disease

Keywords: cardiovascular diseases, diseases of the musculoskeletal system, connective tissue dysplasia, intercellular mediators, childhood diseases

ВИВЧЕННЯ РОЛІ МІЖКЛІТИННИХ МЕДІАТОРІВ У МЕТАБОЛІЗМІ СПОЛУЧНОЇ ТКАНИНИ У ДІТЕЙ З КАРДІОПАТІЄЮ ТА ОСТЕОПЕНІЄЮ

Харківська медична академія післядипломної освіти

С. Б. Павлов, Г. Б. Павлова

Резюме

Вступ. Недиференційовані форми дисплазії сполучної тканини (НДСТ) характеризуються поліорганними змінами і представляють значні труднощі в діагностиці, оцінці прогнозу і можливості корекції. Найбільш значущими проявами НДСТ є зміни опорно-рухового апарату та серцево-судинної системи. Однак до теперішнього часу, не з'ясовані механізми цитокінової регуляції метаболізму СТ, які забезпечують оптимальну міжклітинну взаємодію.

Метою роботи було визначення профілів міжклітинних медіаторів та їх значущість у розвитку порушень загальної схеми регуляції процесів ремоделяції сполучної тканини (СТ) у дітей з кардіопатією та остеопенією.

Матеріали і методи Досліджувану групу склали 80 дітей з кардіопатією та остеопенією віком від 8 до 14 років, хлопчиків – 42, дівчаток – 38. Контрольну групу склали 30 здорових дітей аналогічного віку. Досліджували вміст RANKL, OPG, ІЛ-1 RA, ІЛ-17, TGF-1β, адипонектину та вісфатину у сироватці крові методом імуноферментного аналізу.

Результати дослідження Встановлено, що розвиток остеопенії пов'язаний з дисбалансом у системі: ліганд рецепторного активатора нуклеарного фактора κβ (RANKL)/рецепторний активатор нуклеарного фактора κβ (RANK)/остеопротегерин (OPG), що призводить до активації остеокластогенеза і підвищення кісткової резорбції. Вміст RANKL та OPG у дітей досліджуваної групи був достовірно вищим, ніж в контрольній групі (RANKL - 0.28±0.02 пмоль/л при нормі 0.21±0.02 пмоль/л ($p<0,05$) ; OPG 74.7±3.62 пг/мл при нормі 62.9±2.48 ($p<0,05$)). Спостерігалося порушення адипокінового обміну і зниження продукції цитокіну ІЛ-17, що є прямим індуктором фібробластів. Середні рівні ІЛ-1 RA, ІЛ-17, адипонектину і вісфатину достовірно знижувалися і складали: ІЛ-1 RA - 169±14.2 пг/мл при нормі 264±12.3 пг/мл ($p<0,05$), ІЛ-17 - 13.9±0.43 пг/мл при нормі 30.2±1.26 ($p<0,05$), адипонектин - 18.3±0.23 мкг/мл при нормі 20.9±0.22 мкг/мл ($p<0,05$), вісфатин -158±7.4 нг/мл при нормі 158±7.4 нг/мл ($p<0,05$). Змін в експресії TGF-1β виявлено не було.

Висновки У дітей у дітей із кардіопатією та остеопенією на тлі НДСТ спостерігається дисбаланс в системі регуляції функціональної системи сполучної тканини (ФССТ) на рівні міжклітинних медіаторів, який проявився наявністю патологічної деактивації процесів біосинтезу СТ. Виявлені зміни можуть свідчити про порушення загальної схеми регуляції процесів ремоделювання СТ та зниження резервів адаптації організму, що має відобразитися на подальшій динаміці процесів її ремоделювання та перебігу захворювання.

Ключові слова: серцево-судинні захворювання, захворювання кістково-м'язової системи, дисплазія сполучної тканини, міжклітинні медіатори, дітячі хвороби

Introduction

The structure of cardiovascular and musculoskeletal systems are becoming increasingly important functional disorders and conditions associated with connective tissue dysplasy (CT) manifested the development of cardiomyopathy and osteopeny [7].

Undifferentiated forms of dysplasy CT (UCTD) characterized by multiple organ changes and represent significant difficulties in diagnosis, prognosis assessment and correction capabilities [5, 8,11] .. The high prevalence of CT in the body (50%), and its various functions in almost all physiological and pathological reactions explain simultaneous involvement in the pathological process of multiple body systems [6] and cause a variety of external and visceral manifestations UCTD [1, 27]. The most important of these is the change in the musculoskeletal system. Among UCTD visceral markers to date the most well-known changes in the cardiovascular system [2, 4, 10, 16, 35].

According to modern ideas about the laws of general pathology connective tissue dysplasy should be considered from the standpoint of functional and structural remodeling of all components PT linkages and interactions at the cellular and systemic levels. The main role in the regulation of intercellular relationships play a group of protein molecules called cytokines system. We know that a key part of bone homeostasis are ligand-receptor activator of nuclear factor system kappa-β (RANK), its ligand (RANKL) and osteoprotegerin (OPG) [37], which is responsible for osteoklastohenez, resorption and remodeling of bone tissue.

However, to date, molecular and physiological - biochemical mechanisms of bone and visceral manifestations UCTD until clear. In particular, the mechanisms specified cytokine regulation of metabolism CT, providing optimum intercellular interaction. At the same time, well aware that it is a violation of a regulation device play a major pathogenic role in the formation of pathological process.

Therefore, great interest is the study of pathophysiological and biochemical mechanisms of metabolism and functions CT, determining pathogenetic mechanisms of major developmental abnormalities and syndromes at UCTD.

Objective - determine the profile of intercellular mediators and their significance in the development of common disorders scheme remodelyatsiyi regulation of CT in children with cardiomyopathy and osteopeny.

Materials and Methods

The study involved 80 children with osteopenia and cardiomyopathy who underwent examination and treatment at the Kharkiv Medical Academy of Postgraduate Education (studied group). The children were aged 8 to 14 years. -42 Boys, Girls - 38. The control group consisted of 30 healthy children of similar age. The diagnosis is established according to the results of clinical and anamnestic and laboratory tests.

We investigated the content of RANKL, OPG, IL-1 RA, IL-17, TGF-1β, visfatyn and adiponectin in serum by enzyme immunoassay using test systems produced by "Vector-Best" (Russia).

Statistical analysis was carried out in a package of statistical software Statistica 6.0. The first phase was carried out analysis of distribution curves. If the division was close to normal, the analysis was performed using the methods of variation statistics software package Statistica 6.0 - the statistical method of one-way ANOVA (Fisher LCD post-hoc test). If it is significantly different from normal - differences between the groups were determined by method «Kruskal-Wallis ANOVA and median test». Correlation analysis was performed in the same package Statistica 6.0, using parametric and nonparametric methods, depending on the type of character distribution.

The critical level of significance to test statistical hypotheses by comparing groups — 0,05.

Results and Discussion

In the study content RANKL, OPG, IL-1 RA, IL-17, TGF-1β, and adiponectin visfatyn found the following (Table 1).

Table 1 The content of cytokines in serum in children with cardiomyopathy and osteopenia in comparison with the control group

Indexes	Groups	
	Control	The study group
RANKL, pmol/L	0.21±0.02	0.28±0.02*
OPG, pg/mL	62.9±2.48	74.7±3.62*
IJI-1 RA, pg/ml	264±12.3	169±14.2*
TGF-1β, pg/ml	12.6±0.25	12.6±0.33
IJI-17, pg/ml	30.2±1.26	13.9±0.43*
Adiponectin, mkg/ml	20.9±0.22	18.3±0.23*
Visfatyn, ng/ml	231±10.6	158±7.4*

* - ($p<0,05$) compared with the control group

The average level of RANKL in children with cardiomyopathy and osteopenia was higher than the RANKL control group (Table 1). Median serum RANKL content children of the group amounted to 0.31 (0.17; 0.38) pmol / L (Fig. 1). Increasing the number of RANKL indicates a strengthening bone resorption children of the group.

The average level of OPG in children with cardiomyopathy and osteopenia was also higher than in the controls ($p <0.05$) (Table 1). Median OPG content in children with cardiomyopathy and osteopenia was 65.3 (53.8; 93.51) pg / ml (Fig. 2).

Increased OPG may be due to possible compensatory response to enhance bone resorption. OPG, as protein "receptor-trap" for RANKL, competes with RANK for binding to RANKL. By blocking this process, OPG inhibits bone resorption, bone formation giving priority [9, 17, 29, 32]. Violation binding RANKL and OPG - an essential link in the pathogenesis of diseases that occur with increasing number of RANKL and accompanied by increased bone resorption [23].

We can assume that the violations in RANKL-OPG system in the study group leading to disruption of physiological regulatory mechanisms osteoklastoheneza, activity and longevity of osteoclasts, which interferes with the remodeling ST. It is believed that the nature of remodeling bone is largely defined by OPG and RANKL production [9, 12, 32].

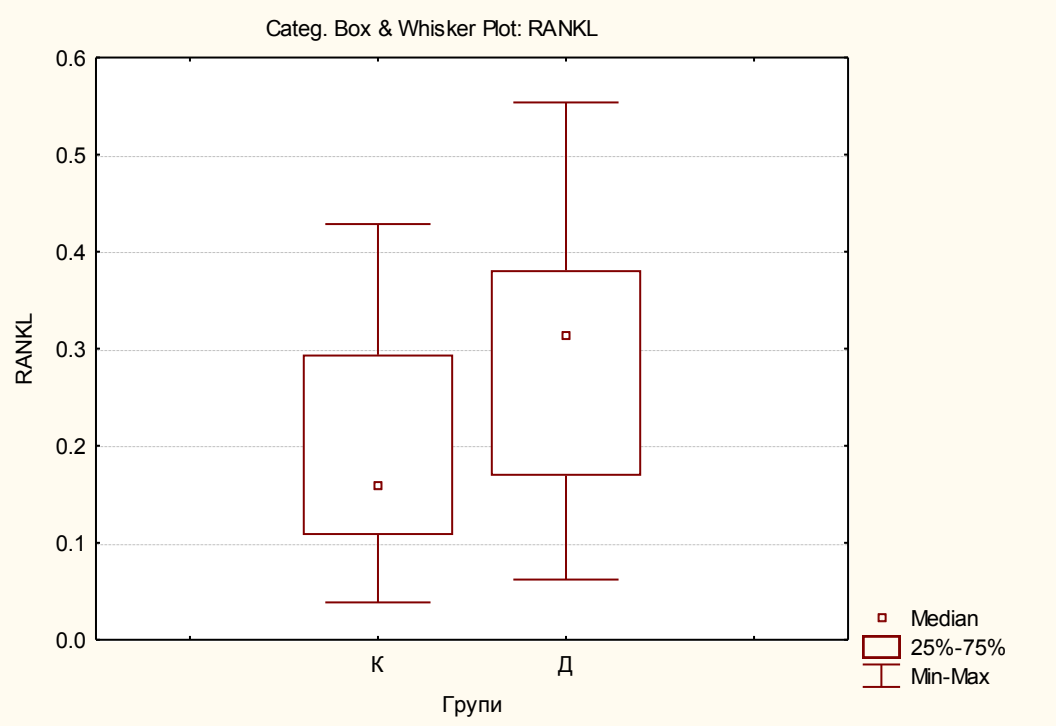

Fig. 1 - Median levels of RANKL in children with cardiomyopathy and osteopeny

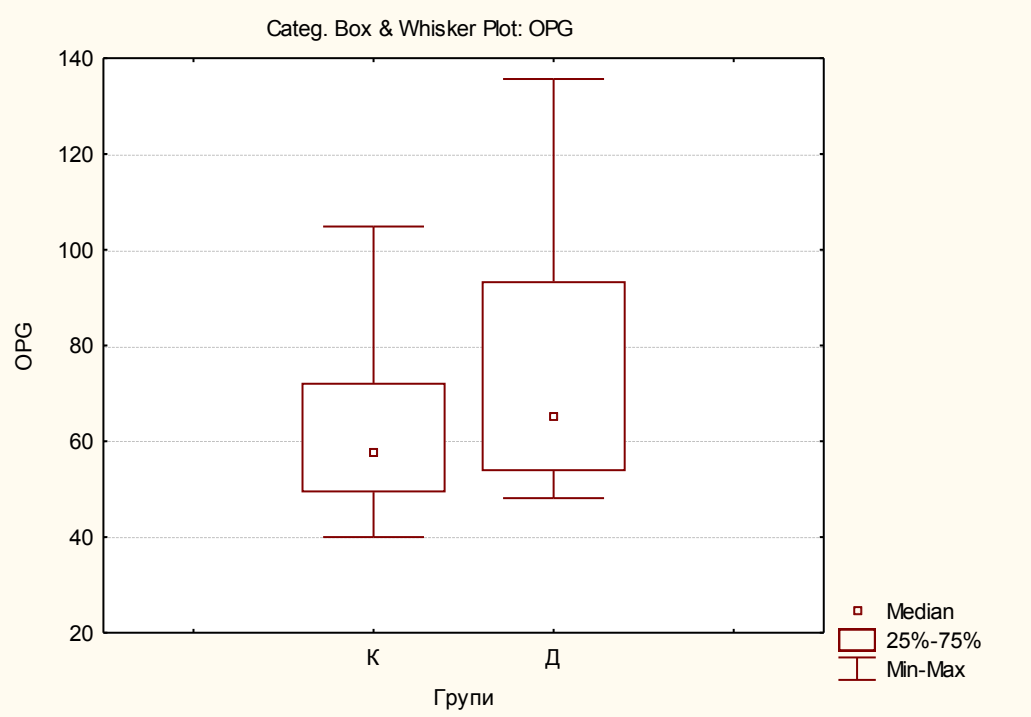

Fig. 2 - Medians OPG levels in children with cardiomyopathy and osteopeny

The average level of IL-1 RA in children with cardiomyopathy and osteopeny was lower than in controls ($p < 0.05$) (Table. 1). Median content of IL-1 RA in children with cardiomyopathy and osteopeny was 164 (86.9; 190) pg / ml (Fig. 3).

Insufficient production of IL-1Ra shows a decline of anti-inflammatory protection. IL-1RA - an important natural anti-inflammatory protein and reducing its content may play a key role in the pathological process in patients of the group. Established that the gene polymorphism IL-1RA associated with an increased risk of fractures with osteoporosis [15].

In healthy tissue IL-1RA synthesized to prevent inflammatory responses mediated by IL-1 and limit further damage to the affected tissue. The effects of IL-1RA as nonsteroidal anti-inflammatory drug can be used in the treatment of chronic inflammatory diseases [3, 14]. Reduced receptor antagonist IL-1 is insufficient to regulate the activity of a powerful inflammatory cytokine IL-1.

Given that IL-1RA mainly producing cells CT (macrophages, monocytes and fibroblasts), violation optimal balance ratio of IL-1RA and IL-1, inevitably leads to disruption of cytokines network and, consequently, the whole UCTD.

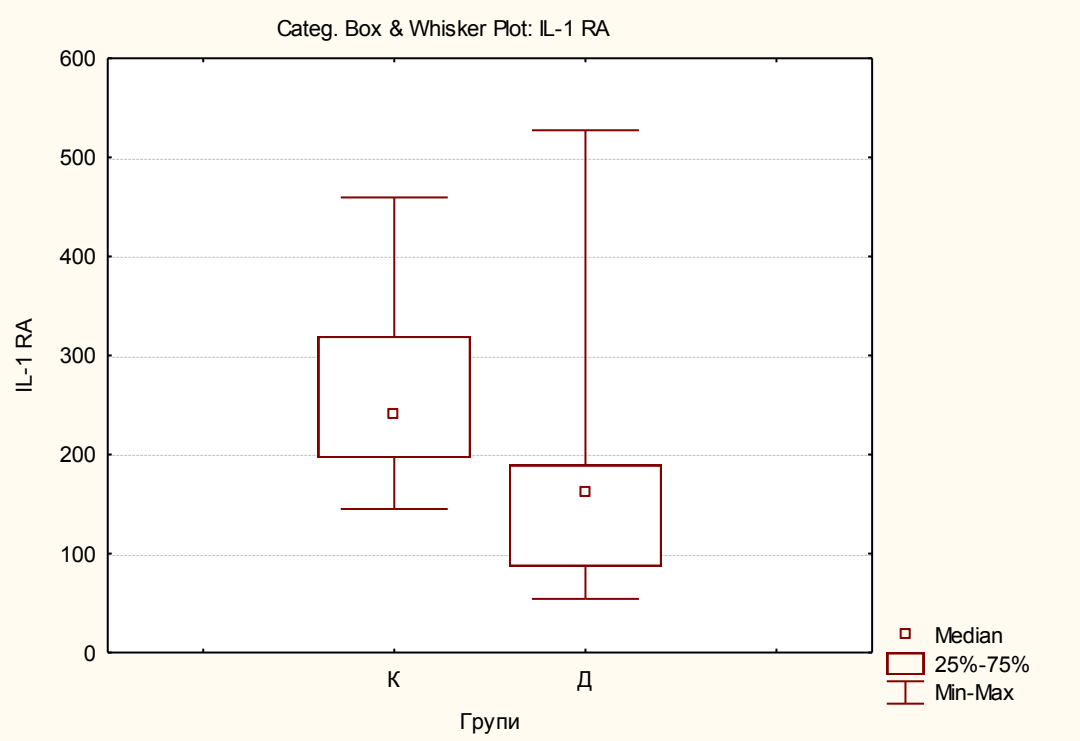

Fig. 3 - Median levels of IL-1RA in children with cardiomyopathy and osteopeny

The average level of TGF-1β in children with cardiomyopathy and osteopeny no different on the level of TGF-1β in control ($p < 0.05$) (tabl.14). Median content of TGF-1β in children with cardiomyopathy and osteopeny was 12.35 (10.2; 14.5) pg / ml (Fig. 4).

It is known that the superfamily of transforming growth factor-b (TGF-β) belongs determining role in the morphogenesis of cartilage and bone [22] signaling pathway TGF-β is a key

element of regulatory mechanisms, formation and degradation of extracellular matrix (ECM) CT [31].

In addition, TGF-β is profibrotychnym cytokine that stimulates the production of proteins in the ECM various organs and systems, over-expression of which leads to tissue fibrosis [25]. Thus, increased expression of TGF-β1 stvorok addition to thickening of heart valves and their dysfunction [20, 36] is the formation of cardiac fibrosis [30, 33], and the increase of ECM proteins in the myocardium - its appearance systolic and diastolic dysfunction [26].

As our study found no change in the expression of TGF-1β children in the study group, we can assume that the change in activity of various components of the signaling pathway TGF-β is associated mainly with a number of inherited disorders century and in many cases shown at UCTD.

It should be noted that the average concentration of this cytokine in the treatment group had a fairly large spread. Perhaps that is why we could not determine the threshold value TGF-β, the excess of which leads to pathological changes. Perhaps the determination of soluble reactive TGF-β1 and TGF-β2 in the serum of patients and evaluation of the relationship between the concentration of TGF-β1 / 2 will be more informative, which requires further research.

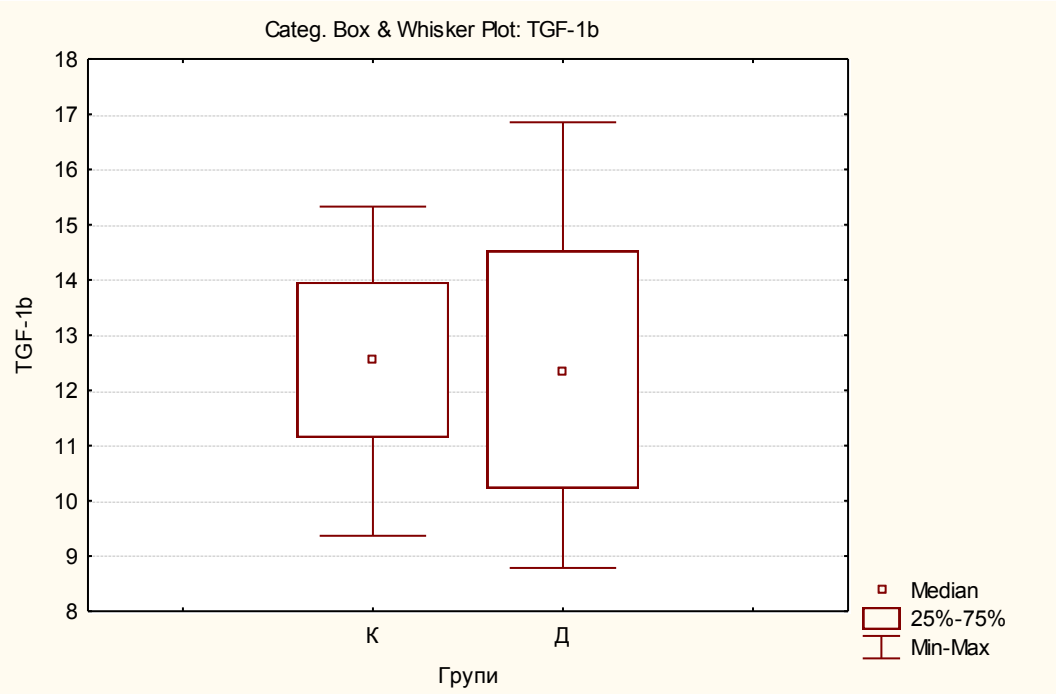

Fig. 4 - Median levels of TGF-1β in children with cardiomyopathy and osteopeny

The children of the group contents of proinflammatory cytokine IL-17, which is a direct inducer of fibroblasts and reflects another signaling pathway activation fibrogenesis [24], was significantly lower than the level of IL-17 in the control ($p < 0.05$) (Table. 1) . Median content of IL-17 in children with cardiomyopathy and osteopeny was 14.3 (12.2; 15.8) pg / ml (Fig. 5). This may indicate the presence of these patients pathological processes deactivating the biosynthesis of

connective tissue, uncharacteristic for its normal condition. The features make it possible to choose the level of IL-17 as an additional criterion of risk violations remodeling CT.

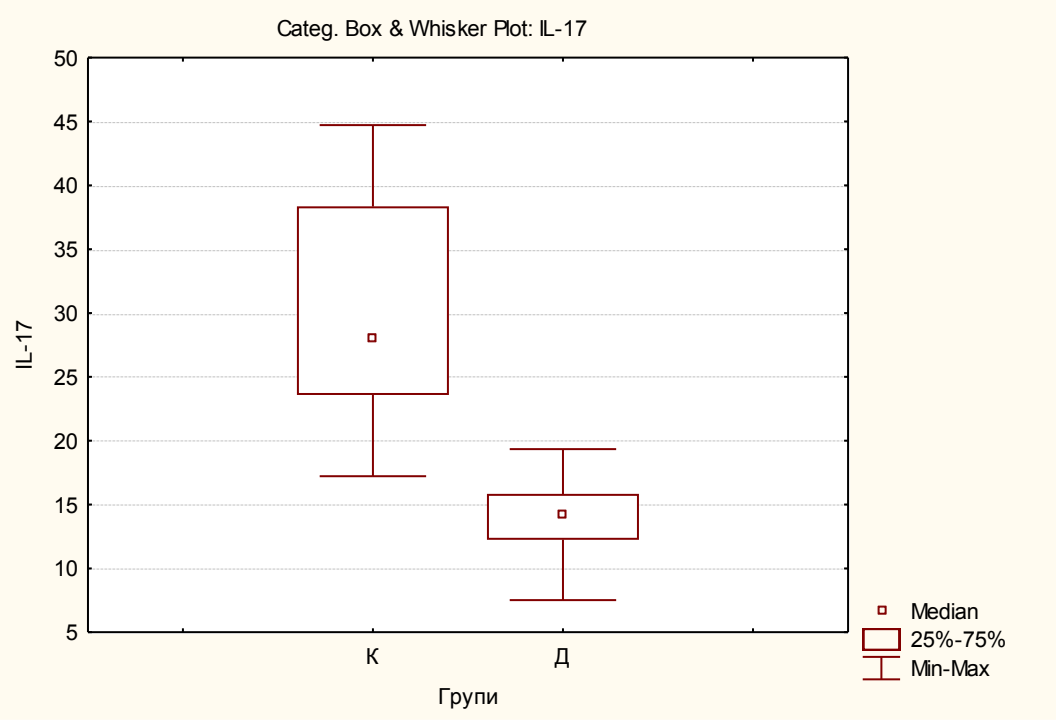

Fig. 5 - Median levels of IL-17 in children with cardiomyopathy and osteopeny

The average level of adiponectin in children with cardiomyopathy and osteopeny was lower than the level of adiponectin in control ($p < 0.05$) (Table 1). Median adiponectin content in children with cardiomyopathy and osteopeny was 18.4 (17.2; 19.6) mg / ml (Fig. 6).

Hipoadyponektynemy may indicate a decrease in anti-inflammatory and antiatherogenic protection for patients of the group. We know that Adiponectin able to participate in the regulation of energy homeostasis and provide anti-inflammatory and antiatherogenic effect as endogenous anhioprotektor [13]. If the damage of the vascular wall he can quickly build up in subendotelial space, thus preventing the expression of adhesion molecules. Depressing the secretion of TNF (tumor necrosis factor), Adiponectin is able to inhibit the development of systemic inflammation [38]. It is believed that the decrease in blood adiponectin is a cause of coronary artery atherosclerosis as well and obesity [21].

Found that children of the group found hipoadypokinemy accompanied by increased levels of RANKL (Table 1). As Adiponectin is a factor in increasing bone resorption and increase the level of factor RANKL [34], reducing its content may be viewed as a compensatory response to hyperproduction RANKL.

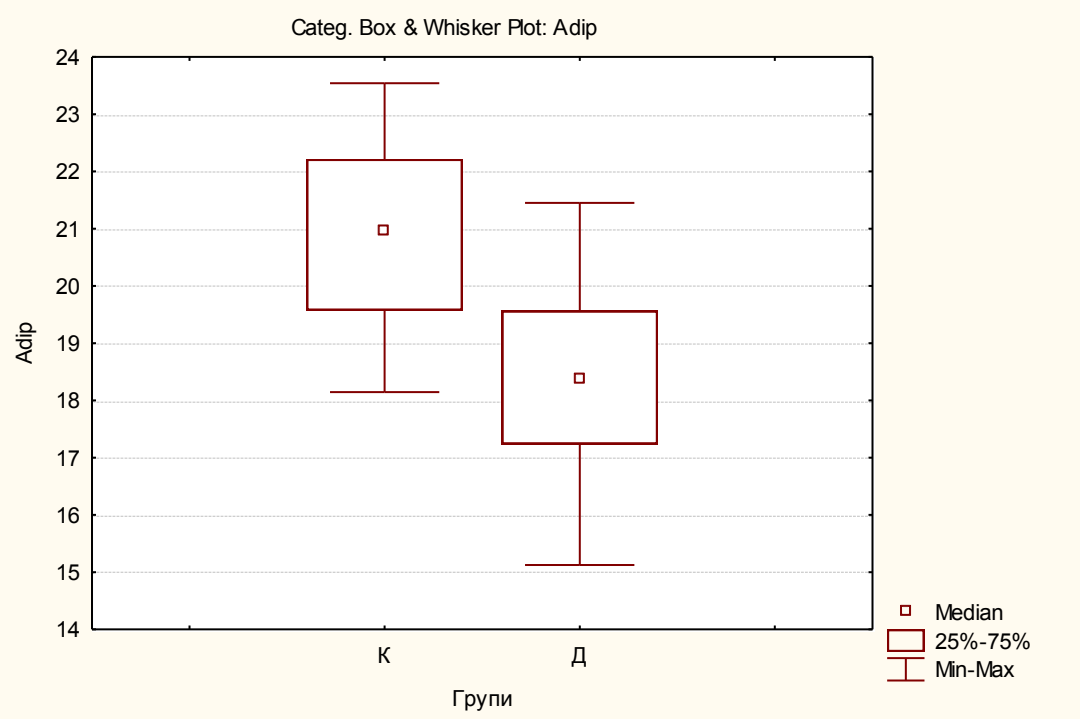

Fig. 6 - Median adiponectin levels in children with cardiomyopathy and osteopeny

Intermediate visfatyn was also lower than the level visfatyn in control ($p < 0.05$) (Table. 1). Median visfatyn content in children with cardiomyopathy and osteopeny was 141 (126, 163) ng / ml (Fig. 7).

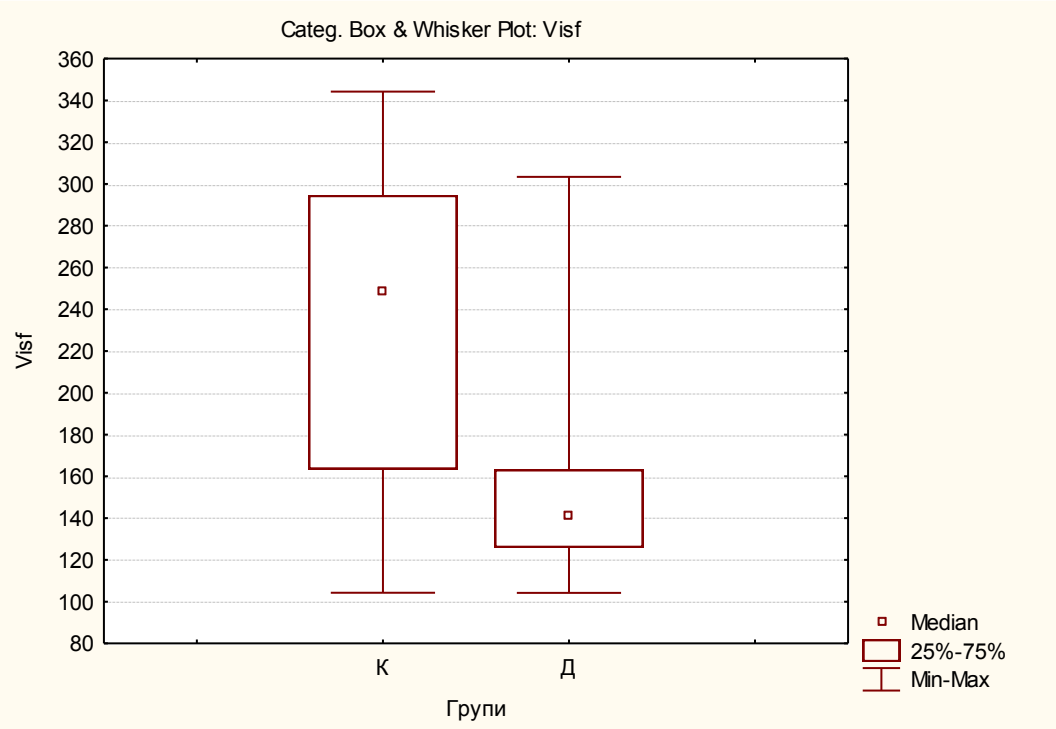

Fig. 7 - Median visfatyn levels in children with cardiomyopathy and osteopeny

An important aspect of the biological role visfatinu imumonomodulyator is its effect. Apart from adipocytes, a significant number of circulating visfatina produced by macrophages. When exposed to the vascular wall inflammatory agents (eg, low-density lipoprotein) visfatinu expression of macrophages at the site of injury significantly increased [18]. Recombinant visfatin activates white blood cells and stimulates synthesis of cytokines (IL-1, IL-6, TNF-a) [28]. Visfatin levels directly correlated with an index of insulin resistance [19].

We can assume that the violations adypokinovoho exchange leading to imbalance in the intercellular mediators FSST dysregulation and the consequent depletion of adaptive reserves.

Results of correlation analysis showed that almost all indicators between cytokine exchange relationships are statistically significant (Table 2).

Table 2 Relationship between cytokine levels in children with cardiomyopathy and osteopeny

	RANKL	OPG	IJI-1RA	TGF-1β	Adiponectin	Visfatyn	IJI-17
RANKL	-	-	-	-	-	-0.47	-0.39
OPG	-	-	-	0.38	0.36	0.58	-
IJI-1RA	-	-	-	0.39	-	-	-0.55
TGF-1β	-	0.38	0.39	-	0.57	-	-0.57
Adiponectin	-	0.36	-	0.57	-	-	-
Visfatyn	-0.47	0.58	-	-	-	-	-
IJI-17	-0.39	-	-0.55	-0.57	-	-	-

In the group of children with cardiomyopathy and osteopeny positive correlation was observed between the levels visfatyn and OPG ($r = 0.58$) ($p < 0.05$), OPG and TGF-1β ($r = 0.38$) ($p < 0.05$), TGF-1β and IL-1RA ($r = 0.39$) ($p < 0.05$), TGF1β and adiponectin ($r = 0.57$) ($p < 0.05$), adiponectin and OPG ($r = 0.36$) ($p < 0.05$) . A negative correlation was observed in the group between the levels of RANKL and visfatyn ($r = -0.47$) ($p < 0.05$), RANKL and IL-17 ($r = -0.39$) ($p < 0.05$), IL-1RA and IL-17 ($r = -0.55$) ($p < 0.05$), TGF1β and IL-17 ($r = -0.57$) ($p < 0.05$).

The revealed changes in the content intercellular mediators may indicate a violation of a framework for the regulation of remodulation ST. This system includes a number of elements, with some key parts of the mechanism, which determine the direction of changes in the relevant parameters act as a sort of flip-flops. Established that the formation multifactorial pathogenesis remodulation ST disorders associated with depletion of reserves adaptation. A combination of

factors contributes to the release of harmful process beyond the physiological adaptation and prevents the system to recover. Defined profiles intercellular mediators in children surveyed indicate a change in the reserves of adaptation that should see the continued dynamic remodeling ST. However, the data require further analysis based polymorphism clinical pathology and pathogenesis of various pathologies ST.

Conclusions

1. Children with cardiomyopathy and osteopenia in the background UCTD there is an imbalance in the system of regulation FSCT at intercellular mediators.

2. The development of osteopeny associated with an imbalance in the system: ligand receptor activator of nuclear factor κβ (RANKL) / receptor activator of nuclear factor κβ (RANK) / osteoprotegerin (OPG), which leads to activation osteoklastoheneza and increased bone resorption.

3. Established that children with cardiomyopathy and osteopeny observed violations adypokins exchange and reduced production of the cytokine IL-17, which is a direct inducer fibroblasts. This may indicate the presence of these patients pathological processes of biosynthesis deactivation CT and be connected with the peculiarities of mechanisms violating its remodeling due to inherited or acquired their character.

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