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## ОСОБЕННОСТИ КЛИНИЧЕСКОГО ТЕЧЕНИЯ ХРОНИЧЕСКОГО ГЕПАТИТА С У БОЛЬНЫХ ИЗ СОЧЕТАННОЙ ПАТОЛОГИЕЙ

### Аннотация

В работе представлены результаты обследования 327 больных хроническим гепатитом С (ХГС). Сформировано 2 группы, среди которых первую группу составили 177 больных ХГС в сочетании с сахарным диабетом 2 типа (СД-2) и вторую группу – 150 больных ХГС без СД-2. Группы были репрезентативны по возрасту, полу и длительностью СД. В результате проведенных исследований у больных СД 2 типа выделены три варианта течения ХГС: первый – с преобладанием типичных симптомов поражений печени – 31% случаев, второй – холестатический в 56% и третий вариант – с выразительными внепеченочными проявлениями в 13% пациентов. При холестатическом варианте ХГС, несмотря на низкую вирусную нагрузку, у 78,8% лиц установлено высокую степень фиброза печени (F3-4), что есть достоверно чаще ( $p < 0,05$ ) в сравнении с другими вариантами. Таким образом, у больных СД-2 наиболее частым есть холестатический вариант ХГС с высокой степенью фиброза печени, что позволяет рассматривать его, как наиболее неблагоприятный в плане развития цирроза печени.

**Ключевые слова:** хронический гепатит С, сахарный диабет, холестатический синдром, фиброз печени.

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## FEATURES OF THE CLINICAL COURSE OF CHRONIC HEPATITIS C OF PATIENTS WITH COMORBIDITY

### Summary

The paper presents the results of the examination of 327 patients with chronic hepatitis C (CHC). Two groups were formed, where the first one consisted of 177 patients with chronic hepatitis C combined with type 2 diabetes (DM-2) and the second group – of 150 patients with chronic hepatitis C without DM-2. The groups were representative by age, sex and duration of diabetes. As a result of undertaken studies there are distinguished three variants of CHC course of patients with type 2 diabetes: the first one is with the predominance of typical symptoms of liver disease – 31% of cases, the second one is cholestatic – 56% and the third variant is with expressive extrahepatic manifestations in 13% of patients. What concerns the cholestatic variant of CHC despite a low viral load, 78.8% of people had a high degree of liver fibrosis (F3-4) which is significantly more frequent ( $p < 0.05$ ) compared to the other variants. Thus, the most frequent is the cholestatic variant CHC with a high degree of fibrosis in patients with type-2 DM, which allows considering it as the most unfavorable in terms of liver cirrhosis development.

**Keywords:** chronic hepatitis C, diabetes mellitus, cholestatic syndrome, liver fibrosis.

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## EXAMINATION OF THE CONNECTIVE TISSUE METABOLISM INDEXES OF PATIENTS WITH REACTIVE ARTHRITIS AND PYELONEPHRITIS

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The aim of this scientific research was to examine connective tissue metabolism indexes of patients with a comorbid course of reactive arthritis and chronic kidney disease. The increase of free hydroxyproline (FOP), hydroxyproline bound with protein (BOP), plasma collagenolytic activity (PCA) and proteolytic activity (PA) have been found in blood what is the evidence of simultaneous synthesis increasing and collagen degradation against a background of collagenase activation. Established significant hexosamine (HA) increase and hexuronic acids (HUA) reduction indicate that glycoproteins' synthesis increased against a background of proteoglycan synthesis decrease. Greatest importance in the diagnostic algorithm of progression and clinical course of reactive arthritis, showed a blood FOP and BOP, HA, degree collagenolytic activity of blood plasma, which showed a direct relationship to the degree of inflammatory activity. Blood FOP, BOP and HA data had the greatest importance in the diagnostic algorithm of progression and clinical course of reactive arthritis. Degrees of blood plasma collagenolytic activity showed direct dependence on inflammation activity degree.

**Keywords:** reactive arthritis, plasma collagenolytic activity, plasma proteolytic activity, hydroxyproline, glycoproteins, proteoglycans.

**The problem, the analysis of research work and publications.** A significant increase of reactive arthritis disease (ReA) is observed all over the world in recent years, what in the overall structure of

rheumatic arthritis disease currently consists 5-11% [1]. ReA incidence is growing simultaneously, that is 30-200 citizens per 100 000 of the adult population [2, 3]. Nowadays, one of the most burning problems

is ReA diagnosis and its treatment [4]. Most of the laboratory findings that are used at ReA diagnosis have not specific character, and reflecting of inflammation process presence and activity [5, 6]. Methods that characterise such connective tissue specific components exchange as collagen and proteoglycan, show more informational content about the progress of pathosis of the affected joints and the extent of reducing the intensity of process under the influence of treatment [7, 8]. Metabolic abnormalities in such system as «proteoglycans and collagen» and change of enzymatic reactions often are preceded by many complications, including chronic kidney disease and renal failure.

**The purpose of the research** is to analyze the connective tissue state of patients with comorbid course of chronic kidney disease and reactive arthritis.

**The main material.** 113 patients have been examined and divided into two groups: in the 1-st group there were patients with Reactive Arthritis (ReA), on its I-III degree of activity and JFI (Joint Functional Insufficiency) on I-III degree (n=65); the 2-nd group consists of patients with ReA and Chronic Kidney Disease (CKD): Pyelonephritis (CP) in the exacerbation phase (n=48). Groups of patients were grouped on age, sex, duration and activity of comorbid diseases. The control group was formed of 20 healthy persons (HP). Metabolism changes of carbohydrate and protein components of the extracellular matrix were determined by the level of free hydroxyproline in (FOP) and hydroxyproline bound with protein (BOP), hexuronic acid (HUA), hexosamine (HA), seromucoid (SM), sialic acid (SA). State of blood plasma proteolytic activity was studied by determining the intensity of lysis azoalbumin (degradation of low

molecular weight proteins), azocasein (proteolysis of high molecular weight proteins), azokol (collagenolysis) («Simko ltd.») and the level of plasma collagenolytic activity (PCA).

The average disease duration was  $24,4 \pm 4,7$  months. Patients average age was  $32,5 \pm 1,2$  years. First group of examined patients consisted of persons (n=50; 76,92%), who have been diagnosed of ReA for the first time, and who had chronic course of disease (n=15; 23,08%). In the group of patients with comorbid course of ReA and CP was observed chronic disease in 79,17% (n=38), and recurrent course in 20,83% (n=10). Leading to the clinical picture of patients in both groups was asymmetrical articular syndrome with joint disease of the upper and lower extremities that was leading in clinical picture of both groups of patients. In most cases, mono- and oligoarthritis were observed. Polyarthritis was approved in patients with chronic ReA against a background of CKD.

During disease exacerbation in patients with ReA level of FOP in blood, what is a marker of collagen catabolism, significantly was higher than in a control group in 1,3 times ( $p < 0,05$ ), while in the second group it was higher in 1,5 times ( $p < 0,05$ ). Simultaneously, the significant increase of BOP in blood was observed in both 1-st and 2-nd in 2,3 and 2,5 times in comparison with HP group ( $p < 0,05$ ), what is the indicator of increased collagen synthesis (table 1). The degree of BOP increase in blood becomes higher with increasing activity in both groups (table 2), as well as the proliferation of «joint insult area» and the evidence of bone changes was determined after ultrasound and pneumoarthrography were made. Free hydroxyproline level in the blood showed a direct correlative dependence on the degree of inflammatory activity

Table 1

Connective tissues indexes in patients with reactive arthritis (M $\pm$ m)

Indexes	HP (n=20)	1-st group (n=65)	2-nd group (n=48)
FOP (mmole/l)	11,61 $\pm$ 0,58	15,16 $\pm$ 0,20 *	17,2 $\pm$ 1,2 */**
BOP (mmole/l)	28,22 $\pm$ 0,4	63,72 $\pm$ 2,36 *	65,7 $\pm$ 3,0 *
HUA (mmole/l)	1,19 $\pm$ 0,07	0,65 $\pm$ 0,33	0,60 $\pm$ 0,21 *
HA (mmole/l)	5,21 $\pm$ 0,31	10,12 $\pm$ 0,24 *	10,56 $\pm$ 0,42*
SA (mmole/l)	2,36 $\pm$ 0,05	4,11 $\pm$ 0,31 *	5,4 $\pm$ 0,2 */**
SM (od units)	0,18 $\pm$ 0,09	0,76 $\pm$ 0,44	0,74 $\pm$ 0,01 *
PCA ( $\mu$ m/h/l)	5,29 $\pm$ 0,06	7,67 $\pm$ 0,26 *	8,02 $\pm$ 0,33 *
PA – azoalbumin (mcg/ml/h)	2,99 $\pm$ 0,28	4,78 $\pm$ 0,54 *	5,23 $\pm$ 0,34 *
PA – azokazein (mcg/ml/h)	2,26 $\pm$ 0,21	4,01 $\pm$ 0,23 *	4,14 $\pm$ 0,25 *
PA – azokol (mcg/ml /h)	0,44 $\pm$ 0,07	0,8 $\pm$ 0,05 *	1,10 $\pm$ 0,05 */**

Note: \* – the difference is accurate in comparison with HP group indexes ( $p < 0,05$ );

\*\* – the difference is accurate in comparison with RA group indexes ( $p < 0,05$ ).

Table 2

Connective tissue index of contents in blood plasma of patients with reactive arthritis depending on the degree of activity (M  $\pm$  m)

Indexes	1-st group (n=65)		2-nd group (n=48)	
	I degree of activity (n=45)	II-III degree of activity (n=20)	I degree of activity (n=18)	II-III degree of activity (n=30)
FOP (mmol/l)	15,06 $\pm$ 0,14	15,36 $\pm$ 0,23	16,49 $\pm$ 0,60 *	18,03 $\pm$ 1,02*/**
BOP (mmol/l)	62,45 $\pm$ 1,21	66,60 $\pm$ 1,43	65,26 $\pm$ 1,41	68,13 $\pm$ 1,50 *
HUA (mmol/l)	0,73 $\pm$ 0,25	0,47 $\pm$ 0,13	0,74 $\pm$ 0,18	0,52 $\pm$ 0,21
HA (mmol/l)	10,01 $\pm$ 0,24	10,35 $\pm$ 0,11	10,41 $\pm$ 0,20	10,65 $\pm$ 0,39
PCA ( $\mu$ m/h/l)	7,55 $\pm$ 0,26	7,92 $\pm$ 0,16	7,79 $\pm$ 0,33	8,20 $\pm$ 0,23
PA-azoalbumin (mcg/ml/h)	4,46 $\pm$ 0,25	5,49 $\pm$ 0,24	5,05 $\pm$ 0,33	5,39 $\pm$ 0,32
PA-azokazein (mcg/ml/h)	3,89 $\pm$ 0,25	4,26 $\pm$ 0,23	3,98 $\pm$ 0,31	4,25 $\pm$ 0,25
PA-azokol (mcg/ml/h)	0,78 $\pm$ 0,07	0,85 $\pm$ 0,05	1,05 $\pm$ 0,05	1,12 $\pm$ 0,07*/**

Note: \* – the difference is accurate in comparison with the 1-st group of patients with RA indexes on I degree of activity ( $p < 0,05$ );

\*\* – the difference is accurate in comparison with the 1-st group of patients with RA indexes on II-III degrees of activity ( $p < 0,05$ ).

as compared with the level of sialic acid ( $r=0,704$ ;  $p<0,01$ ) and seromucoid ( $r=0,585$ ;  $p<0,01$ ).

During the study of both 1-st and 2-nd groups there was observed a statistically significant increase of HA content almost in 2,0 times compared to the control group ( $p<0,05$ ). A significant HUA decrease was determined in 2-nd group of patients compared to the control group ( $p<0,05$ ), but in the 1-st group HA content had a tendency to decrease (table 1). Was established the inverse correlation of medium strength between level of HA and HUA in the blood ( $r = -0,366$ ,  $p < 0,01$ ). In most cases asymmetric mono- or oligoarthritis of upper and lower joints with a domination of II-III degree of activity was determined in most cases (85,0%) at patients who have ReA with comorbid chronic pyelonephritis.

In the 2-nd group it was determined the impact of comorbid chronic pyelonephritis over the ReA activity increase, in comparison to RA isolated course in terms of inflammation and connective tissue reaction: leukocytosis, increased erythrocyte sedimentation rate (ESR) ( $p<0,05$ ), levels of C-reactive protein in blood in 2,5 times, ( $p<0,05$ ), sialic acids in 1,3 times ( $p<0,05$ ), seromucoid in 1,6 times ( $p<0,05$ ), fibrinogen on 11,2% ( $p<0,05$ ), globulin on 25,5% ( $p<0,05$ ), decrease of albumin in blood at 19,6% ( $p<0,05$ ), BOP in 1,2 times, and PA in 1,4 times ( $p<0,05$ ) (table 3). All these obtained results point to the CP active formation phase within ReA activity.

Patients of 1-st and 2-nd groups showed a significant increase of PCA indicators in 1,4 times and 1,5 times in comparison to as HP group ( $p<0,05$ ). Lysis of low molecular weight protein growth in patients with ReA was observed in comparison to the control group: at the 1-st group in 1,6 times, at the 2-nd in 1,7 times ( $p<0,05$ ). Such intense proteolytic degradation of macromolecular proteins underwent changes, and this degradation was higher than the control in 1,8 times in both groups ( $p<0,05$ ). A significant increase of azokol lysis at the 1-st and the 2-nd group was determined during the study of plasma collagenolytic activity in comparison to the control group in 1,8 times and 2,5 times ( $p<0,05$ ), where in the indicator exceeded in 1,4 times in the second group compared to the individuals of the first tested group ( $p<0,05$ ).

Parallel growth of BOP and FOP simultaneously can be an indicator of collagen synthesis increase and collagen degradation, and the formation of weakened collagen.

The inverse correlation of medium strength between level of HA and HUA in the blood can be indicator of glycoprotein synthesis increase on the background of proteoglycan synthesis decreased. As far as hexosamine is a part both of proteoglycans and glycoproteins, so its increase in the blood can be indicator of decay enhancement of connective tissue carbohydrate-protein components. Increase of HA is a factor that activates inflammation and abnormal bacterioagglutinin formation. Longstanding inflammation of connective tissue causes its degradation. Increase of HA advances changes of other indexes which characterize the functional status of the connective tissue. Increase of the average level of HA in blood is determined when conventional laboratory methods are not more informative. A progressive increase of HA content in both groups was already determined at II-III degree of activity. There is a significant pathogenetic relation between metabolic proteoglycans and immunological disorders processes in this group of patients (Amirahmadi S. F. et al., 2004). Metabolic products of connective tissues ground substance have antigenic specificities and are able to stimulate immune reactions in tissues (Lysenko I. V., 2006), and may have a significant impact on the overall health and quality of life of the affected individuals. The investigation of the metabolism of connective tissue specific components exchange as collagen and proteoglycan in patients with reactive arthritis, show more informational content about the progress of pathosis of the joints and the extent of reducing the intensity of process under the influence of treatment, prognostic significance in the diagnosis of other organ damage, especially kidneys.

**Conclusions.** Examination of the connective tissue state in patients with comorbid course of reactive arthritis and chronic kidney disease showed a significant increase of free and bound with protein hydroxyproline levels in blood, collagenolytic and proteolytic activity in plasma, what is indication of simultaneous increase of synthesis and collagen degradation on the background of collagenolysis activation. Determined significant increase of hexosamine and hexuronic acid content decrease indicates point to the increase glycoproteins synthesis against a background of decreased proteoglycans synthesis. Greatest importance in the diagnostic algorithm of progression and ReA clinical course

**Clinical and biochemical blood analysis indexes in patients with reactive arthritis depending on the degree of activity ( $M \pm m$ )**

Table 3

Indexes	1-st group (n=65)		2-nd group (n=48)	
	I degree of activity (n=45)	II-III degree of activity (n=20)	I degree of activity (n=18)	II-III degree of activity (n=30)
Hemoglobin (g/l)	142,4 $\pm$ 2,2	130,4 $\pm$ 2,1*	115,8 $\pm$ 2,0*	105,4 $\pm$ 1,8*/**
Erythrocyte ( $\times 10^{12}/l$ )	4,6 $\pm$ 0,2	3,8 $\pm$ 0,1*	4,0 $\pm$ 0,2*	3,2 $\pm$ 0,1*/**
Leucocyte ( $\times 10^9/l$ )	10,3 $\pm$ 0,5	13,2 $\pm$ 0,6*	13,0 $\pm$ 0,3*	15,6 $\pm$ 0,2*/**
ESR (mm/h)	12,9 $\pm$ 0,5	18,7 $\pm$ 0,7*	16,5 $\pm$ 0,9*	39,8 $\pm$ 0,8*/**
CRP (mg/l)	4,6 $\pm$ 2,5	25,6 $\pm$ 3,1*	18,1 $\pm$ 3,7*	64,6 $\pm$ 2,7**
Sialic acids (mmol/l)	3,6 $\pm$ 0,1	4,3 $\pm$ 0,2*	4,2 $\pm$ 0,1*	5,4 $\pm$ 0,2*/**
Fibrinogenous (g/l)	4,1 $\pm$ 0,1	5,0 $\pm$ 0,2*	4,6 $\pm$ 0,1*	5,9 $\pm$ 0,2*/**
Whole protein (g/l)	73,7 $\pm$ 1,1	78,7 $\pm$ 1,0*	70,3 $\pm$ 1,2	63,7 $\pm$ 1,0*/**
Albumins (%)	56,2 $\pm$ 0,6	48,4 $\pm$ 1,1*	45,0 $\pm$ 1,1*	39,5 $\pm$ 1,0*/**
Globulins (%)	43,8 $\pm$ 0,6	51,6 $\pm$ 0,6*	55,0 $\pm$ 0,8*	60,5 $\pm$ 0,6*/**
A/G	1,28 $\pm$ 0,03	0,94 $\pm$ 0,04*	0,82 $\pm$ 0,02*	0,65 $\pm$ 0,02*/**

Note: \* – the difference is accurate in comparison with the 1-st group of patients with RA indexes on I degree of activity ( $p<0,05$ );

\*\* – the difference is accurate in comparison with the 1-st group of patients with RA indexes on II-III degrees of activity ( $p<0,05$ ).

have such indicators as levels of free and bound with protein hydroxyproline in blood, hexosamine and degree collagenolytic activity of blood plasma (intensity of azocol lysis), what showed a direct relation to the degree of inflammation activity. Increase of ReA activity degree was found in the group of patients with comorbid course of reactive arthritis and chronic pyelonephritis in comparison

to isolated ReA case in terms of inflammation and connective tissue reaction.

**Future research prospects:** to study and propose a new method in the diagnosis of reactive arthritis and development on its background of chronic pyelonephritis based on the cluster and classification analysis methods and construct practical recommendations that can be used in clinical practice.

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## ДОСЛІДЖЕННЯ МЕТАБОЛІЗМУ СПОЛУЧНОЇ ТКАНИНИ У ХВОРИХ НА РЕАКТИВНИЙ АРТРИТ І ПІСЛОНЕФРИТ

### Анотація

Метою даного дослідження було вивчити особливості метаболізму сполучної тканини у хворих із коморбідним перебігом хронічної хвороби нирок та реактивного артрити. Було встановлено вірогідне підвищення вмісту в крові вільного оксипроліну (ВОП), білковозв'язаного оксипроліну (БЗОП), показників колагенолітичної (КЛА) та протеолітичної активності плазми (ПАК), що свідчить про одночасне підсилення синтезу та розпаду колагену на тлі активації колагенолізу. Встановлене достовірне підвищення гексозамінів (ГА) та зменшення вмісту гексуроно-вих кислот (ГК) вказує на підсилення синтезу глікопротеїнів на тлі зниження синтезу протеогліканів. Найбільшу значущість у діагностичному алгоритмі прогресування та клінічний перебіг реактивного артрити мали показники у крові ВОП та БЗОП, ГА, ступеню колагенолітичної активності плазми крові (інтенсивність лізису азоколу), котрі показали пряму залежність від ступеня активності запального процесу.

**Ключові слова:** реактивний артрит, колагенолітична активність плазми, протеолітична активність плазми, оксипролін, глікопротеїни, протеоглікани.

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## ИССЛЕДОВАНИЕ МЕТАБОЛИЗМА СОЕДИНИТЕЛЬНОЙ ТКАНИ У БОЛЬНЫХ НА РЕАКТИВНЫЙ АРТРИТ И ПИЕЛОНЕФРИТ

### Аннотация

Целью данного исследования было изучить особенности метаболизма соединительной ткани у больных с коморбидным течением хронической болезни почек и реактивного артрита. Было установлено достоверное повышение содержания в крови свободного оксипролина (СОП), биологически связанного оксипролина (БСОП), показателей колагенолитической (КЛА) и протеолитической активности плазмы (ПАК), что свидетельствует об одновременном усилении синтеза и распада коллагена на фоне активации колагенолиза. Установлено достоверное повышение гексозаминов (ГА) и уменьшение содержания гексуроновых кислот (ГК) указывает на усиление синтеза гликопротеинов на фоне снижения синтеза протеогликанов. Наибольшую значимость в диагностическом алгоритме прогрессирования и клиническое течение реактивного артрита имели показатели в крови СОП и БСОП, ГА, степени колагенолитической активности плазмы крови (интенсивность лизиса азокола), которые показали прямую зависимость от степени активности воспалительного процесса.

**Ключевые слова:** реактивный артрит, колагенолитическая активность плазмы, протеолитическая активность плазмы, оксипролин, гликопротеины, протеогликаны.