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PROTEIN OXIDATIVE MODIFICATION AND BONE EROSIONS IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS: WHAT'S IN COMMON?

The aim of the present study was to investigate the was to determine the intensity of carbonyl stress in early rheumatoid arthritis (eRA) with an evaluation of its relationship with the pathogenesis of inflammatory and erosive processes. Aldehyde- and ketonephenylhydrazones were estimate as markers of free radicals activation. The antibodies to citrullined peptide, tumor necrosis factor-alpha were determined by immune-enzyme assay. Subjects with clinically significant concurrent diseases or conditions were carefully excluded during the patient's selection. Data processing and analysis were performed, by using a statistical software packages «SPSS 16.0 for Windows» and «Statistica for Windows 7.0» (StatSoft Inc.). The level of statistical significance was taken as $p < 0,05$. Study results shown, that the patients with eRA characterized increase of free radicals generation, according to level of phenylhydrazones, early markers of oxidative processes. Thus, our findings suggest that in eRA there is a pronounced imbalance between the activity of the processes of generation of free radicals and their elimination under the influence of endogenous antioxidant systems (superoxide dismutase) are characterized by substantial predominance of the activity of free radicals with the intensification of the processes of oxidative transformation of protein molecules at the carbonyl stress.

Oxidative stress is an important factor in the pathogenesis of early rheumatoid arthritis (eRA) [1]. Continuous generation of reactive oxygen species in joints of patients with activated neutrophils and macrophages, as well as through iterative processes, cycles of hypoxia-reperfusion in joints, leading to damage to the synovial cells, the destruction of cartilage and bone erosions [2–5].

In recent years, the concept of essential pathogenic role of oxidative stress on the cell damage caused by immune inflammation was launched [6–9]. In addition, special attention is paid to the pathogenic role of reactive oxygen species and initiated by the lipid peroxidation processes in the development and progression of inflammatory destructive processes in patients with eRA [10–15].

Free oxygen radicals, generated by monocytes, synovial macrophages, accumulate toxic products of lipid peroxidation and in low endogenous antioxidant cause matrixdepolymerization of connective tissue, both directly and through the activation of proteolytic enzymes, matrix metalloproteinases (MMP), violate the synthetic processes in fibroblasts and chondrocytes, cause the development of subcartilaginous erosions, activated leukocyte collagenase encourage the development of apoptosis and necrosis of endothelial cells, chondrocytes [4]. All of these disorders can severely or completely disrupt the functioning of cells and the organism as a whole, to worsen the patient's condition.

However, in addition to lipids in the lipid peroxidation, the process of free radical intensely involved and other classes of organic compounds. Of particular importance among them are proteins. Moreover, in the literature there are indications of a greater sensitivity to oxidation are proteins than lipids [16, 17].

Given this, according to precisely assess the oxidative modification of proteins, it is very important to expand existing concepts of pro-oxidant processes in the mechanisms of cartilage and bone damages in eRA. The evaluation of free association and the severity of damage biomolecules destructive and erosive lesions of the cartilage in RA in the literature almost doesn't occur.

This study is the first to determine association between carbonyl stress, oxidative modification of proteins and early bone erosions.

PATIENTS AND METHODS

Between December 2009 and April 2011, 156 patients with eRA (according to the preliminary ACR/EULAR definition) were surveyed (98 women and 58 men) and had active disease as defined by a disease activity score evaluated in 28 joints (DAS28) $\geq 3,2$.

Inclusion criteria were as follows: age $49,79 \pm 2,04$ years, more than two swollen joints for >6 weeks and <6 months. Baseline characteristics did not differ significantly between the cohorts. The study included patients without severe visceral pathology and associated diseases that

could restrict to additional metabolic disturbances and affect the investigated parameters. A control group consisted of 67 apparently healthy persons.

Blood samples from RA patients were analysed for titres of IgM-RF by ELISA using kits from Immulisa, MMP-3 tumor necrosis factor-alpha (TNF- α), anti-cyclic citrullinated peptide (anti-CCP) method of the immune-enzyme analysis according to the annexed diagnostic sets of instructions. X-ray joint study (Larsen index) [1] was used to assess the bone erosions: evaluated the proximal interphalangeal joints, 2 thumb joints, 10 metacarpophalangeal joints and wrists.

Level of products of oxidative modification of proteins — aldehydesphenylhydrazone (APH) and ketonephenylhydrazone (KPH) was defined as the baseline (spontaneous activity) and after stimulation. To initiate the oxidative modification of proteins using Fenton's substratum (0.1 M phosphate buffer, pH 7.4, 1 mMFe²⁺ +, 0,3 mMH₂O₂). To determine the oxidative modification of proteins was carried out prior to deposition with a 20% solution of three chloroacetic acid (TCA).

The test values are presented as follows: the sample mean \pm standard error of the mean. Normality of distribution was assessed by Kolmogorov-Smirnov criteria (D), Lilliefors and Shapiro-Wilk (W). If the distribution differs from the normal, or the analysis of ordinal variables used the Mann-Whitney U for 2 unrelated samples for a larger number of samples, criteria of Kruskal-Wallis H with further comparison to Games-Howell.

Comparison groups on the basis of qualitative binary performed using χ^2 test with the analysis of contingency tables. The presence and severity of statistically significant differences between the indices was evaluated by means of univariate analysis of variance on the circuit and then comparing groups Sheffe. The null hypothesis that the layers of expectation sample rejected if the ratio of the residual variance organized exceed critical Fisher's criteria (Fkr.) with an appropriate number of degrees of freedom with a significance level of less than 0.05. To assess the relative influence of the factor values underlying the group of other factors that affect effective sign out a calculation of the determination coefficient (h^2).

Results of the study are processed using the statistical package licensed program «Statistica for Windows 6.0» (StatSoft Inc., № AXXR712D833214FAN5) at the Department of Medical Informatics ZSMU and «SPSS 16.0», «Microsoft Excel 2003» Separate statistical procedures and algorithms are implemented in the form of specially written macros in the relevant programs. For all types of analysis were considered statistically significant differences at a significance level $p < 0.05$.

RESULTS AND DISCUSSION

We evaluated the dynamics of the presence and severity of oxidative stress indicators in patients with eRA. According to the distribution, the data are characterized by properties of normal, Gauss, distribution. Similarly, do not differ from the normal distribution, the frequency of occurrence of changes were characteristic for the other parameters, reflecting the process of oxidative protein conformational variability. The level of production of free radicals, obtained in the study, demonstrated a significant increasing in the group of patients with eRA compared with the control group values as spontaneous and metal-induced oxidative modification of proteins, blood plasma level of phenylhydrazone (PH) (an increase of APH to 104.35% and 158.95%, and KPH almost 3 and 2.6 times respectively achieved significance level less than 0.05 in all cases).

These changes (elevation as early (APH) and late (KPH)), while increasing concentrations of these parameters induced oxidative destruction of protein molecules) are accompanied by a credible reduction of antioxidant capacity, as evidenced by the reduction of superoxide dismutase (SOD) at 63.44% when compared with the control. Next, we analyze the changes in the parameters of oxidative modification of proteins depending on the degree of expression of MMP-3. In patients with total MMP-3 50 ng/ml (2 subgroup) a statistically significant excess of both APH and KPH (measured spontaneous oxidation) to 36.04% and 33.84% when compared to the same period subgroups of patients with eRA with the values of MMP-3 is not greater than 50 ng/mL, respectively. Induced oxidation was also significantly higher in the 2 groups at 58.90% and 46.90%, respectively, than in the first (Table 1).

Table 1

Activity of antioxidant systems in RA patients of different groups depending on the degree of expression of MMP-3

| Indicators | RA patients | | | Control 4 (n=52) | The magnitude of differences between groups, % | | | |
|--------------------------------|------------------------------|--------------------------------|--|---------------------|--|-------------------|---------|---------|
| | Up to 50 ng/ml 1 (n=32) | More than 50 ng/ml 2 (n=83) | In total for eRA patients 3 (n=115) | | 1 and 2 | 1 and 4 | 2 and 4 | 3 and 4 |
| | APH spont., USL. u/g protein | 0.111 \pm 0.003* | 0.151 \pm 0.002** | | 0.14 \pm 0.002* | 0.069 \pm 0.002 | 36.04 | 60.87 |
| APH stimulus, USL. u/g protein | 0.198 \pm 0.007* | 0.265 \pm *0.003* | 0.246 \pm 0.004* | 0.095 \pm 0.002 | 33.84 | 108.42 | 178.95 | 158.95 |
| KPH spont., USL. u/g protein | 0.073 \pm 0.005* | 0.116 \pm 0.003** | 0.104 \pm 0.003* | 0.035 \pm 0.004 | 58.90 | 108.57 | 231.43 | 197.14 |
| KPH stimulus, USL. u/g protein | 0.113 \pm 0.004* | 0.166 \pm 0.005** | 0.151 \pm 0.003* | 0.057 \pm 0.006 | 46.90 | 98.25 | 191.23 | 164.91 |
| ODS, e/mg/min | 61.49 \pm 0.86* | 37.72 \pm 0.52** | 52.77 \pm 0.47* | 88.27 \pm 0.57 | -63.02 | -30.34 | -57.27 | -40.22 |

*Reliability of differences ($p < 0.05$) when compared with similar control.

**Reliability of differences ($p < 0.05$) when compared with similar patients with eRA on MMP-3 more than 50 pg/mL.

Study of the SOD dynamics depending on the expression of MMP-3 also showed that activity increases, proteinase complex, there was a reduction on 63%. It is important to note, that this decreasing was associated with a significant increasing in parameters of stimulated oxidative protein modification. These changes indicate a depletion of the reserve-adaptation capabilities of the organism and decreasing stability in pathological activation of the free-radical processes in conditions of oxidative-antioxidant imbalance.

As the presented data analysis processes of oxidation and the activity of antioxidant systems in patients with eRA according to the length of the underlying disease, it is shown that as the length of the verification eRA increased both spontaneous and stimulated, oxidative modification of plasma proteins on the level of PH (marked increasing in the history of more than 10 years as an APH (for basal) of 12.7%, and to a greater extent, KPH form at 15.22% and 18.64%, respectively). The level of serum antioxidant activity was minimum in subgroup two 11.12% less reporting of subgroups one and 51.74% below the level of antioxidant protection. Thus, in the subgroup with a duration of more than 10 years, hypertension, registered maximum values, reflecting the intensity of the oxidation processes in a parallel decrease in antioxidant serum capacity ($p < 0.05$), indicating a strong pro-antioxidant imbalance.

We also analyzed the dynamics of the parameters characterizing the oxidative modification of protein molecules, depending on the degree of eRA activity. It is important to note, that in patients with varying degrees of activity, parameters characterizing the intensity of oxidation-reduction mechanisms, were significantly different (see Figure).

There was a progressive increasing in the indices, in particular the quantitative characteristics of the oxidative degradation of plasma proteins on the level of PH. Also registered regressing of SOD in eRA with increasing inflammation, but no significant differences in static specified index was achieved when comparing those with 1 and 3, the degree of activity of eRA (-52.41%). Also, due to the large spread, the statistical difference between the KPH, depending on the intensity of the disease was also not recorded, although it should be noted that if eRA patients with minimal activity — this indicator was only 107.31% less, the patients with severe activity-differences were already 216.83%, val-

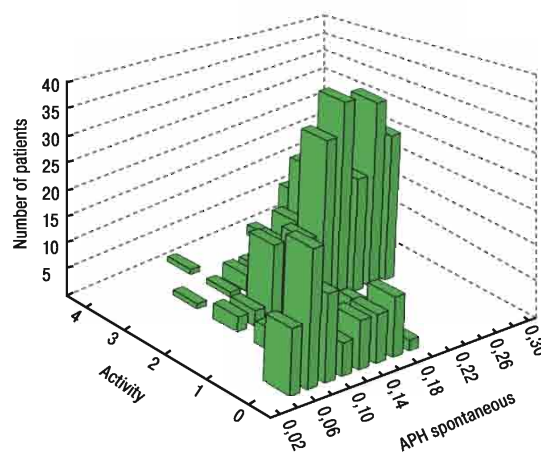


Figure. Dynamics of APH spontaneous depending on the activity of the disease

ues of antioxidant activity of this group patients (lower quartile was 15 s.u.) were significantly lower than normal values.

Evolution of the parameters oxidative modification of proteins, according to the radiological stage of eRA, was of mixed: without undergoing significant changes in the two groups at 1 and 2 stages. Differences for the KPH without induction were more pronounced and were -20.37% and -19.63% ($p < 0.05$). Dynamics of serum antioxidant reserve of the subject also proved reliable predictor.

Noted, that patients with eRA augments progressively the severity of violations of redox homeostasis, as eloquently illustrated how the data changes in the structure of proteins initially and after induction of metal, especially the APH and regressing to an intensification of the generation of free radicals in oxidative stress. Further, in order to evaluate the effect of free radical oxidation activation of biomolecules on the dynamics of immune-inflammatory processes and the severity of the bone erosions in eRA, we've conducted analysis of variance (ANOVA) (table 2).

The very high value of the F-ratio 30.193 index and the close functional relationship between the APH and anti-CCP, as evidenced by relatively high figure calculated empirical correlation ratio (0.58). Also found a statistically significant effect oxidative modification to a resultant variable as TNF- α . In the corresponding dispersion complex, the reported APH spontaneous reliably

Table 2

The results of ANOVA of influence of free radical mechanisms (according to APH spontaneous) to the level of inflammatory processes and the number of bone erosions

| Factor | Dispersion | SS | Degrees of latitude | MS | F | p | η^2 | η |
|---------------|------------|------------|---------------------|----------|--------|--------|----------|--------|
| Anti-CCP | intergroup | 725,467 | 1 | 725,467 | 30,193 | <0,001 | 0,335 | 0,579 |
| | residual | 1441,638 | 60 | 24,027 | — | — | | |
| | general | 2167,105 | 61 | — | — | — | | |
| TNF- α | intergroup | 0,011 | 1 | 0,011 | 15,317 | <0,001 | 0,282 | 0,531 |
| | residual | 0,028 | 38 | 0,001 | — | — | | |
| | general | 0,039 | 39 | — | — | — | | |
| Larsen Index | intergroup | 4524,745 | 1 | 4524,745 | 10,072 | 0,003 | 0,201 | 0,449 |
| | residual | 17 969,146 | 40 | 449,229 | — | — | | |
| | general | 22 493,891 | 41 | — | — | — | | |

SS – sum of squares; MS – the average sum of squares; dl – number of degrees of latitude; F – F-value ratio Fisher; p – reached the significance level of differences, η^2 – specific value impact factor underlying the group of a set of factors that affect the effective sign; η – empirical correlation ratio.

account for about 53% of the variation in the values of TNF $\eta = 0.28$ and $F = 15.32$, indicating a relationship between the degree of intensification of carbonyl stress in eRA and the severity of immunopathology processes. The results of the calculation of the dispersion relations and the proportion of the total variance, which is influenced by APH on the Larson's index: 10.07 and 20% at $p = 0.003$. Moreover, consideration of the functional dependence by calculation of the empirical correlation ratio (0.45) allowed to establish a close relationship between the studied features.

Oxidative stress acts as one of the leading factors of joint tissue damage in eRA, and the mechanisms are in direct effect, and indirectly, through the activation the inflammatory cascade. The results show, that the patients with eRA have the activation of peroxidation processes, which causes the development of metabolic disorders, changes in the cell membrane and the formation of erosions [11, 13].

Thus, the data obtained allow to conclude, that there is a marked imbalance between eRA activity generating free radicals and their elimination under the influence of endogenous antioxidant systems, characterized by significant prevailing activity of free radicals and oxidative stress status.

ОКСИДАТИВНАЯ МОДИФИКАЦИЯ БЕЛКОВ И КОСТНЫЕ ЭРОЗИИ У БОЛЬНЫХ РАННИМ РЕВМАТОИДНЫМ АРТРИТОМ: ЧТО ОБЩЕГО?

В.Н. Коваленко, Д.Г. Рекалов, Н.П. Красько

Резюме. Цель исследования — определение интенсивности карбонильного стресса при раннем ревматоидном артрите (рРА) с оценкой его патогенетической взаимосвязи с воспалительно-эрозивным процессом. Альдегидные и кетонные формы дигидрофенилгидразонов были оценены в качестве маркеров активации свободных радикалов. Антитела к цитруллинированному пептиду, фактору некроза опухоли- α определяли иммуноферментным анализом. Лица с клинически значимыми сопутствующими заболеваниями или состояниями были тщательно исключены. Обработка и анализ данных проводили с помощью статистических пакетов программ «SPSS 16 для Windows» и «Statistica для Windows 7.0» (StatSoftInc.). Уровень статистической значимости принят $p < 0,05$. Результаты исследования показали, что пациенты с РА характеризуются увеличением свободной генерации радикалов, согласно уровню альдегидных и кетонных формы дигидрофенилгидразонов, ранних маркеров окислительных процессов. Полученные данные позволяют сделать вывод, что у больных рРА при активации воспалительного процесса происходит активация процессов пероксидации в рамках карбонильного стресса, что вызывает развитие дистрофических и деструктивных изменений в хрящевой ткани с нарушением обмена протеогликанов и формирование эрозий.

Ключевые слова: ранний ревматоидный артрит, фенилгидразон, матриксные металлопротеиназы, супероксиддисмутаза.

ОКСИДАТИВНА МОДИФІКАЦІЯ БІЛКІВ ТА КІСТКОВІ ЕРОЗІЇ У ХВОРИХ НА РАННІЙ РЕВМАТОЇДНИЙ АРТРИТ: ЩО СПІЛЬНОГО?

В.М. Коваленко, Д.Г. Рекалов, М.П. Красько

Резюме. Мета дослідження — визначення інтенсивності карбонільного стресу при ранньому ревматоїдному артриті (рРА) з оцінкою його патогенетичного взаємозв'язку із запально-ерозивним процесом. Альдегідні й кетонні форми дигідрофенілгідразонів були оцінені в якості маркерів активації вільних радикалів. Антитіла до цитрулінованого пептиду, фактору некрозу пухлини- α визначали імуноферментним аналізом. Особи з клінічно значущими супутніми захворюваннями чи станами були ретельно виключені. Обробку та аналіз даних проводили за допомогою статистичних пакетів програм «SPSS 16.0 для Windows» і «Statistica для Windows 7.0» (StatSoftInc.). Рівень статистичної значущості прийнятий $p < 0,05$. Результати дослідження показали, що пацієнти з РА характеризуються збільшенням вільної генерації радикалів, згідно рівню альдегідних і кетонних форм дигідрофенілгідразонів, ранніх маркерів окисних процесів. Отримані дані дозволяють зробити висновок, що у хворих на рРА при активації запального процесу відбувається активація процесів пероксидації в рамках карбонільного стресу, що викликає розвиток дистрофічних і деструктивних змін у хрящовій тканині з порушенням обміну протеогліканів і формування ерозій.

Ключові слова: ранній ревматоїдний артрит, фенілгідразон, матриксні металлопротеїнази, супероксиддисмутаза.

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РЕФЕРАТИВНА ІНФОРМАЦІЯ

Существует ли резистентность к ацетилсалициловой кислоте?

Подготовил В.Г. Безшейко

В ходе изучения феномена резистентности к ацетилсалициловой кислоте (АСК) группа американских ученых из университета Пенсильвании (University of Pennsylvania), Филадельфия, США, во главе с доктором Тилом Гроссером (Tilo Grosser) получили неожиданные результаты. Исследователи сообщают, что на практике резистентность к АСК является следствием замедленного высвобождения кишечнорастворимой формы препарата.

Указанные данные получены на выборке из 400 здоровых некурящих добровольцев в возрасте 18–55 лет. Обследуемых разделили на 3 группы с назначением АСК в обычной форме и оценкой ответа на этот препарат спустя 8 ч после его приема (1-я группа, n=40); АСК в кишечнорастворимой форме и оценкой ответа спустя 8 ч (2-я группа, n=210); АСК в кишечнорастворимой форме и оценкой ответа спустя 4 ч (3-я группа, n=150).

У всех 40 пациентов, принимавших АСК в обычной форме, наблюдали ответ на препарат в виде редукции агрегации тромбоцитов >60%. Во 2-й и 3-й группах доля пациентов, не ответивших на препарат, составила 17 и 49% соответственно.

После первого тестирования 108 испытуемых, не ответивших на применение АСК в кишечнорастворимой форме, после периода вымывания препарата, обеспечившего его полное выведение из организма, приняли АСК в обычной форме. Остальные добровольцы приняли ту форму АСК, которую принимали ранее.

Результаты второго тестирования эксперимента показали, что все пациенты, не ответившие на прием кишечнорастворимой АСК, ответили на АСК в обычной форме. В то же время некоторые пациенты 2-й и 3-й групп, у которых не выявлено ре-

зистентности к изучаемому препарату в первом тесте, не ответили на его применение во втором тесте. Эти данные, по мнению Т. Гроссера, не подтверждают существование фенотипа резистентности к АСК.

В третье тестирование включили 27 добровольцев, которые не ответили на прием АСК в кишечнорастворимой форме в предыдущих тестированиях. Им снова назначили кишечнорастворимую АСК, но на этот раз в низкой дозировке и на 7-дневный курс с целью имитации профилактического приема АСК, рекомендуемого при различных заболеваниях. 25 испытуемых, которые в предыдущих тестированиях ответили на прием АСК, составили группу контроля.

В результате на третьем тестировании только 1 доброволец из экспериментальной группы не ответил на терапию. В то же время в контроле такой исход наблюдали у 2 испытуемых.

Таким образом, по мнению Т. Гроссера, основываясь на полученных данных, можно сделать вывод о том, что если «истинная» резистентность к АСК и существует, то этот феномен является крайне редким. Причины, по которым прием АСК не оказывает должного действия, могут быть различными. В первую очередь речь идет о применении кишечнорастворимых форм с замедленной абсорбцией в желудочно-кишечном тракте, что продемонстрировано в исследовании, а также взаимодействии АСК с другими препаратами.

Также Т. Гроссер отметил, что достичь желаемого ответа при применении кишечнорастворимой АСК можно, однако это займет некоторое время, что может повлиять на комплаенс.

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