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Enzyme markers of periodontal tissue remodeling activity and the immunological profile of saliva in adolescents with juvenile idiopathic arthritis

Background. Analysis of oral fluid parameters in patients with inflammatory periodontal diseases and juvenile idiopathic arthritis (JIA) may help to identify new markers in gingivitis diagnostics.

Aim: to investigate the levels of acid and alkaline phosphatases, immunoglobulins of class A, M, G in oral fluid and the value of the mineralization index in adolescents with JIA, depending on the basic medical support of the disease, JIA subtype, the state of individual oral hygiene and the intensity of gingival inflammation.

Materials and methods. 80 children aged 10 to 17 years with JIA and 20 adolescents without comorbidities were included in the research. Basic dental examination with plaque staining, assessment of inflammation severity using the PMA index, and oral fluid sampling to determine acid and alkaline phosphatase activity, mineralization index, and Ig A, M, and G titers were performed. The participants were classified into five categories depending on: presence or absence of JIA, type of basic pharmacological therapy (patients whose treatment regimen includes methotrexate (MTX) at a dosage of ≤ 15 mg ($n = 43$), greater than 15 mg ($n = 18$), or a combination of MTX and adalimumab ($n = 19$) and the control group ($n = 20$)), JIA subtype (polyarticular RF+ ($n = 29$) and RF- ($n = 10$), undifferentiated ($n = 5$), oligoarticular ($n = 24$), enthesitis-associated ($n = 12$), and comparison group ($n = 20$)), level of individual oral hygiene based on the PHP index values (excellent ($n = 3$), good ($n = 28$), satisfactory ($n = 37$) and poor ($n = 12$)), and level of gingival inflammation according to the value of the PMA index (mild gingivitis ($n = 52$) and moderate ($n = 28$)) (the last two classifications were applied only to patients with JIA).

Results. The presence of JIA, its subtype, and the pharmacological treatment do not affect the activity of acid and alkaline phosphatase, the value of the mineralization index, IgA and M titers, but they do affect the IgG titer: patients with JIA, those undergoing treatment with MTX ≤ 15 mg and adalimumab, and those with oligoarticular JIA had higher IgG titers compared to the control group by 1.57, 1.6 and 1.8 times, respectively. No influence of gingival inflammation severity or individual oral hygiene status on the analyzed indicators was found among patients with JIA.

Conclusion. The identified patterns contribute to the expansion of existing knowledge on the course of inflammatory periodontal diseases in the context of JIA and may serve as a basis for developing targeted dental prevention programs for this patient group.

Keywords: Adolescents, Oral Fluid, Idiopathic Arthritis, Acid Phosphatase, Alkaline Phosphatase, Immunoglobulin.

Background. Responding to the challenges of today, one of the key vectors of modern dentistry development is currently the study of the state of periodontal tissues in patients with general somatic diseases. Thus, Kapila YL emphasizes the presence of multi-link cross-links and factors that connect the main periodontal diseases and systemic diseases and conditions [1].

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease with unknown etiology, which manifests in childhood and is characterized by damage to peripheral joints [2]. The features of its course certainly arouse interest among dental scientists in the context of determining the state of periodontal tissues in patients with JIA and encourage the

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search for potential risk factors that can be used as predictors of the development of severe forms of inflammatory processes in the gums of this patient category.

The analysis of literature data performed by Tang J *et al.* aimed to demonstrate the impact of JIA on the state of periodontal tissue, revealing that patients in this category are more prone to dental plaque deposition and have a higher risk of gingivitis and periodontitis [3].

In our opinion, the above trends highlight the necessity of saliva analysis in patients with JIA in the context of searching for potential biomarkers of periodontal disease development, and the obtained data can be used during the development of a comprehensive dental prevention program for this category of patients.

Koppolu P. *et al.* (2021) describe the mechanism of the body's reaction to the development of periodontal tissue pathology mainly by enzymes produced by various inflammatory and bacterial cells, resulting in tissue degradation. Acid and alkaline phosphatases titers are known biomarkers to be changed in patients with periodontal diseases [4].

Sur L.M. *et al.* (2019) defined JIA as a "classic" autoimmune process [5], which allows us to assume the presence of potential changes in the immunoglobulin profile of saliva in this category of patients. Therefore, the study of these indicators is relevant and may contribute to expanding the understanding of the features of the course of inflammatory processes in periodontal tissues in patients of this group.

Aim: to investigate the levels of acid and alkaline phosphatases, immunoglobulins of class A, M, G in oral fluid and the value of the mineralization index in adolescents with JIA, depending on the basic medical support of the disease, JIA subtype, the state of individual oral hygiene and the intensity of gingival inflammation.

MATERIALS AND METHODS

The study was performed at the Department of Pediatric Cardiorheumatology of the State Institution "Institute of Child and Adolescent Health" of the National Academy of Medical Sciences of Ukraine. 80 children aged 10 to 17 years with JIA who take specific medications according to the protocols in the specialty "Pediatric Cardiorheumatology" were included in this research. The control group consisted of 20 adolescents without general somatic pathology. At the stage of involvement in the study, all participants, their parents or caregivers filled out and signed a voluntary informed consent to participate in research. The study design was reviewed and approved by the Bioethics Commission of Kharkiv National Medical University (protocol №2 from October 12, 2022)

Each participant underwent a basic dental examination with supragingival plaque dyeing using Shiller-Pysarev colouring solution with assessment of the level of individual hygiene using the Patient Hygiene Performance (PHP) index. The index value corresponded to

one of four levels of oral hygiene: 0 – excellent level, from 0.1 to 1.7 – good, from 1.8 to 3.4 – satisfactory, and more – poor. The intensity of gingival inflammation was assessed using the papillary-marginal-alveolar index PMA (in the Parma modification). The obtained percentage value of the index corresponded to the following levels of intensity of the inflammatory process in the gums: up to 30% – mild degree of gingivitis, 31-50% – moderate, and more – severe degree of gingivitis.

To determine the level of acid and alkaline phosphatases, immunoglobulins of classes A, M, and G, unstimulated saliva was collected by passive salivation from 9 to 12 o'clock. Patient preparation consisted of instructions to avoid drinks and foods with a high content of sugar, acids or caffeine before the investigation, to avoid the meal an hour before the study and to rinse the oral cavity 10 minutes before the collection of biological material. Within 30 minutes after collection, samples were frozen and stored at -80°C immediately before analysis [6]. Analysis of the content of acid and alkaline phosphatases, immunoglobulins of classes A, M and G was carried out using the reagent set "Alkaline phosphatase-kin. SpL", "Acid phosphatase-kin. SpL" and "Ig A, M, G-IFA" (LLC "Laboratory Granum", Kharkiv, Ukraine). The mineralization index was calculated by dividing the alkaline phosphatase concentration by the acid phosphatase value for each study participant [7]. The statistical data set was processed in the STATISTICA 10.0 program.

The distribution of participants in the study occurred five times. Within the first distribution, two groups were created according to the presence (n=80) or absence (n=20) of JIA in the patient. The second division concerned the basic medical support of the rheumatological disease: adolescents undergoing a course of treatment with methotrexate (MTX) in a dosage of less than or equal to 15 mg (n=43) and greater than this dosage (n=18), patients whose treatment regimen includes MTX and adalimumab (n=19) and the control group (n=20). The third distribution into groups was based on variants of the course of rheumatological disease: polyarticular rheumatoid factor (RF) negative (RF-) (n=10), polyarticular rheumatoid factor positive RF+ (n=29), enthesitis-associated (n=12), undifferentiated (n=5), oligoarticular (n=24) subtypes of JIA and a group of healthy individuals (n=20). The last two divisions were carried out within the group of patients with JIA. Based on the results of the assessment of the level of individual oral hygiene using the PHP index, 4 groups were formed: with excellent (n=3), good (n=28), satisfactory (n=37) and poor (n=12) levels of oral hygiene. According to the results of the analysis of the PMA index, the following groups were formed: JIA patients with mild gingivitis (n=52) and moderate gingivitis (n=28). In each of the distributions presented above, patients were comparable by sex and age.

To analyse the nature of the distribution of quantitative characteristics in the analyzed samples, the Shapiro-Wilk (*W* test) and Kolmogorov-Smirnov methods were used. In case of declining the theory of normality of the data distribution in the sample, data was presented in the format of the median and interquartile range *Me* (*Lq*; *Uq*). The analysis of the presence of statistically significant differences in quantitative values in independent groups was carried out as follows: in the case of comparison of two groups – using the Mann-Whitney *U*-test (UMV), in the case of three or more groups, the Kruskal-Wallis *H*-test was used with posterior pairwise comparisons using UMV. The results obtained were considered statistically significant with $p < 0.05$, with an adjusted value for multiple comparisons using the corrections Holm-Bonferroni and Benjamini-Hochberg. Correlation analysis was performed using Spearman's rank correlation test. The correlation was assessed as

direct or inverse, its strength was assessed according to the modulus of the *r* value: less than 0.2 – very weak, up to 0.5 – weak, less than 0.7 – medium, up to 0.9 – high, greater than 0.9 – very high.

RESULTS AND DISCUSSION

The analysis of oral fluid in patients with JIA compared with children without concomitant general somatic pathology did not reveal statistically significant differences between the activity of acid and alkaline phosphatase, the value of the mineralization index and the titers of IgA and IgM. At the same time, the UMV test with $p = 0.001$ allows us to conclude that in this study adolescents with JIA had an IgG titer 1.54 times higher compared to children in the control group, which in our opinion can be regarded as a marker of increased activity of the non-specific defense system of periodontal tissues against infections caused by periodontal pathogens (Table 1).

Table 1. Immunological profile of oral fluid and main biochemical markers of bone tissue activity in children with JIA and the control group

	Patients with JIA (n = 80)	Controls (n = 20)	p UMV
Alkaline phosphatase U/L	17,050 (14,300;24,250)	15,400 (12,100;19,250)	0,36
Acid phosphatase U/L	9,750 (0,988;1,468)	10,625 (8,075;22,500)	0,54
Mineralization index, c.u.	1,800 (0,976;2,805)	1,542 (0,643;1,965)	0,13
Ig A, g/L	0,920 (0,715;1,335)	0,797 (0,680;1,326)	0,80
Ig M, g/L	0,598 (0,485;0,846)	0,520 (0,398;0,707)	0,13
Ig G, g/L	6,848 (5,306;11,554)	4,450 (2,318;7,132)	0,001

The Spearman rank correlation test allowed us to distinguish the following correlations in the group of patients with JIA: a direct relationship of average activity between acid and alkaline phosphatase titers was observed ($r = 0.502$, $p < 0.05$), a direct weak relationship between alkaline phosphatase concentration and IgG level ($r = 0.246$, $p < 0.05$), an inverse high correlation between acid phosphatase level and mineralization index value ($r = -0.77$, $p < 0.05$), a weak direct correlation between acid phosphatase level and IgG titer ($r = 0.28$, $p < 0.05$). Also, within the framework of the analysis, a direct weak correlation between IgA and IgM levels was detected ($r = 0.312$, $p < 0.05$).

In the control group of children and adolescents, the following relationships were found: a direct medium correlation between the levels of acid and alkaline phosphatase ($r = 0.66$, $p < 0.05$), the level of alkaline phosphatase and IgG ($r = 0.52$, $p < 0.05$), an inverse weak correlation between the levels of acid phosphatase and the value of the mineralization index ($r = -0.44$, $p < 0.05$) and direct medium-strength correlations between the level of acid phosphatase and the value of IgG ($r = 0.637$, $p < 0.05$) and the titers of IgA and IgM ($r = 0.52$, $p < 0.05$).

At the next stage of the study, the analyzed indicators were studied depending on the basic medical support. As a result, we did not find a pronounced effect of the drugs used in the treatment of JIA on the titers of acid and alkaline phosphatase, the value of the mineralization index and the activity of IgA and IgM.

However, the results of the Kruskal-Wallis test *H* (3, $N = 100$) = 14.65, $p = 0.0021$ state a statistically significant effect of the basic medical support on the value of IgG. A series of posterior pairwise comparisons using UMV allows us to conclude that patients who are treated with MTX at a dosage of less than or equal to 15 mg demonstrate, on average, 1.57 times higher IgG titers compared to the values obtained in the control group. Patients treated using adalimumab demonstrate 1.6 times higher values of the above-mentioned indicator compared to adolescents without somatic pathology. The obtained results indicate that patients undergoing treatment with the above-mentioned drugs demonstrate increased activity of the periodontal tissue protection system against periodontal pathogens compared to that of children in the control group (Table 2). A series of Spearman rank correlation tests was conducted to search for correlations between quantitative indicators. Thus, patients undergoing treatment with MTX ≤ 15 mg had a direct correlation of medium strength between the concentrations of acid and alkaline phosphatase in the oral fluid of patients in this group ($r = 0.55$, $p < 0.05$), a high inverse correlation was found between acid phosphatase titers and the value of the mineralization index, a direct weak correlation between the value of the mineralization index and the values of Ig A ($r = 0.3$, $p < 0.05$) and Ig M ($r = 0.375$, $p < 0.05$), as well as directly between IgM and IgA titers ($r = 0.338$, $p < 0.05$).

Table 2. Immunological profile of oral fluid and main biochemical markers of bone tissue activity depending on the type of JIA drug therapy

	Alkaline phosphatase U/L	Acid phosphatase U/L	Mineralization index, c.u.	Ig A, g/L	Ig M, g/L	Ig G, g/L
JIA patients, taking MTX ≤15 mg (n = 43)	17,600 (14,300;34,100)	9,750 (6,000;29,250)	1,907 (0,976;2,724)	0,826 (0,688;1,220)	0,533 (0,460;0,822)	7,006 (5,586;11,623)
JIA patients, taking MTX >15 mg (n = 18)	16,500 (14,300;20,900)	8,125 (5,750;18,500)	2,011 (0,907;3,300)	1,081 (0,793;2,178)	0,694 (0,511;0,862)	5,809 (2,676;9,861)
JIA patients, taking MTX and adalimumab (n = 19)	17,600 (9,900;24,200)	11,000 (6,500;21,500)	1,304 (0,900;2,558)	0,927 (0,733;1,331)	0,635 (0,450;0,948)	7,231 (5,383;12,854)
Controls (n = 20)	15,400 (12,100;19,250)	10,625 (8,075;22,500)	1,542 (0,643;1,965)	0,797 (0,680;1,326)	0,520 (0,398;0,707)	4,450 (2,318;7,132)
Kruskal- Wallis test	p = 0,499	p = 0,76	p = 0,296	p = 0,54	p = 0,26	p = 0,0021
A series of posterior tests for Ig G: $p_{\text{MTX} \leq 15 \text{ mg} - \text{MTX} > 15 \text{ mg}} = 0,067$; $p_{\text{MTX} \leq 15 \text{ mg} - \text{adalimumab}} = 0,939$; $p_{\text{MTX} \leq 15 \text{ mg} - \text{controls}} = 0,0004^*$; $p_{\text{MTX} > 15 \text{ mg} - \text{adalimumab}} = 0,107$; $p_{\text{MTX} > 15 \text{ mg} - \text{controls}} = 0,169$; $p_{\text{adalimumab} - \text{controls}} = 0,0054^*$ * - statistically significant p value corrected using Holm-Bonferroni method.						

In the group of patients whose treatment regimen used MTX >15 mg, the following correlations were found: direct relationships of medium strength between IgG and alkaline phosphatase titers ($r = 0.556$, $p < 0.05$) and IgA and IgM concentrations ($r = 0.595$, $p < 0.05$); there was also a very high inverse correlation between acid phosphatase concentration and mineralization index value ($r = -0.91$, $p < 0.05$). Analysis of correlations in the group of patients treated with adalimumab revealed direct relationships of medium strength between acid and alkaline phosphatase concentrations ($r = 0.61$, $p < 0.05$) and IgG and IgM titers ($r = 0.626$, $p < 0.05$). Also in this group, there is an inverse relationship of medium strength between the

values of acid phosphatase and the mineralization index ($r = -0.57$, $p < 0.05$).

Assessment of the influence of the JIA subtype on the change in alkaline and acid phosphatase titers, the value of the mineralization index and IgA and IgM indices did not confirm the presence of such. However, the Kruskal-Wallis test $H(5, N = 100) = 15.18$, $p = 0.0096$ revealed a statistically significant influence of the JIA subtype on the concentration of IgG in the oral fluid. A series of posterior pairwise comparisons using UVM allows us to conclude that patients with an oligoarticular subtype of JIA demonstrate, on average, 1.8 times higher IgG titers compared to controls (Table 3).

Table 3. Immunological profile of oral fluid and main biochemical markers of bone tissue activity depending on the type of JIA subtype

	Alkaline phosphatase U/L	Acid phosphatase U/L	Mineralization index, c.u.	Ig A, g/L	Ig M, g/L	Ig G, g/L
JIA polyarthritis RF+ (n = 29)	19,800 (14,200;26,400)	11,000 (6,250;24,750)	1,584 (0,975;2,724)	1,053 (0,760;1,339)	0,592 (0,511;0,801)	6,767 (5,239;9,220)
JIA polyarthritis RF- (n = 10)	14,300 (13,200;15,400)	6,125 (4,500;9,500)	2,015 (1,379;3,178)	0,764 (0,662;1,433)	0,583 (0,407;1,214)	7,724 (5,154;14,340)
JIA enthesitis-related (n = 12)	15,950 (14,300;20,300)	11,250 (6,750;16,750)	1,837 (0,918;2,724)	0,869 (0,722;1,970)	0,755 (0,447;1,126)	5,624 (2,609;11,280)
JIA undifferentiated (n = 5)	15,400 (15,400;15,400)	6,250 (5,250;21,250)	2,724 (2,464;3,242)	0,822 (0,810;0,826)	0,781 (0,669;0,870)	6,160 (5,383;12,854)
JIA oligoarthritis (n = 24)	21,450 (15,400;36,350)	21,250 (6,750;34,125)	1,606 (0,917;2,535)	0,910 (0,706;1,195)	0,527 (0,482;0,789)	8,111 (6,144;13,077)
Controls (n = 20)	15,400 (12,100;19,250)	10,625 (8,075;22,500)	1,542 (0,643;1,965)	0,797 (0,680;1,326)	0,520 (0,398;0,707)	4,450 (2,318;7,132)
Kruskal-Wallis test	p = 0,124	p = 0,156	p = 0,483	p = 0,862	p = 0,51	p = 0,0096
$p_{\text{poly RF} + - \text{poly RF} -} = 0,585$; $p_{\text{poly RF} + - \text{enth-rel}} = 0,289$; $p_{\text{poly RF} + - \text{undif}} = 0,789$; $p_{\text{poly RF} + - \text{oligo}} = 0,14$; $p_{\text{poly RF} + - \text{controls}} = 0,0092$; $p_{\text{poly RF} - - \text{enth-rel}} = 0,29$; $p_{\text{poly RF} - - \text{undif}} = 0,903$; $p_{\text{poly RF} - - \text{oligo}} = 0,82$; $p_{\text{poly RF} - - \text{controls}} = 0,0387$; $p_{\text{enth-rel} - \text{undif}} = 0,246$; $p_{\text{enth-rel} - \text{oligo}} = 0,07$; $p_{\text{enth-rel} - \text{controls}} = 0,228$; $p_{\text{undif} - \text{oligo}} = 0,525$; $p_{\text{undif} - \text{controls}} = 0,0894$; $p_{\text{oligo} - \text{controls}} = 0,0003^*$ * - statistically significant p value corrected using Benjamini-Hochberg method.						

Assessment of correlations in each of the studied groups using a series of Spearman rank correlation tests allowed us to obtain the following results. In the group of patients with polyarticular RF+ variant of JIA, certain patterns were found: a direct average relationship between alkaline and acid phosphatase levels ($r = 0.53$, $p < 0.05$), a high-strength inverse relationship between acid phosphatase titer and mineralization index value ($r = -0.77$, $p < 0.05$), as well as a weak direct relationship between IgA titer and mineralization index value ($r = 0.47$, $p < 0.05$). Adolescents with polyarticular RF- subtype of JIA demonstrated correlations between indicators in the form of a very high-strength inverse relationship between acid phosphatase value and mineralization index ($r = -0.96$, $p < 0.05$), a direct average relationship between IgA and IgM titers ($r = 0.648$, $p < 0.05$). In children with enthesitis-associated variant of JIA, a very strong inverse correlation was found between the acid phosphatase level and the mineralization index

value ($r = -0.93$, $p < 0.05$), while in the group of patients with the undifferentiated variant of the disease, no correlation was found. The group of patients with oligoarticular course of JIA demonstrated a strong inverse correlation between the acid phosphatase level and the mineralization index value ($r = -0.73$, $p < 0.05$), a weak inverse correlation between the acid phosphatase level and the concentration of IgM in oral fluid ($r = -0.43$, $p < 0.05$), and a weak direct correlation between the IgM titer and the mineralization index value ($r = 0.497$, $p < 0.05$).

The assessment of the influence of the level of individual oral hygiene on the markers of oral fluid was carried out using a series of Kruskal-Wallis tests. The results did not reveal statistically significant differences in the levels of acid and alkaline phosphatase, the values of the mineralization index and basic immunoglobulins in oral fluid depending on the fact that the adolescent with JIA belonged to the group according to the level of individual oral hygiene (Table 4).

Table 4. Immunological profile of oral fluid and main biochemical markers of bone tissue activity depending on the state of personal oral hygiene in patients with JIA

	Alkaline phosphatase U/L	Acid phosphatase U/L	Mineralization index, c.u.	Ig A, g/L	Ig M, g/L	Ig G, g/L
Patients with an excellent level of individual oral hygiene (n=3)	16,500 (11,000;24,200)	8,000 (4,250;9,750)	2,482 (2,063;2,588)	0,530 (0,392;1,415)	0,345 (0,324;0,521)	2,472 (2,428;5,586)
Patients with a good level of individual oral hygiene (n=28)	19,750 (14,850;25,350)	16,375 (6,375;24,690)	1,410 (0,816;2,411)	0,788 (0,675;1,377)	0,559 (0,473;0,772)	7,219 (4,507;10,114)
Patients with a satisfactory level of individual oral hygiene(n=37)	14,300 (13,200;23,100)	7,430 (5,500;21,750)	2,200 (1,004;2,916)	1,053 (0,822;1,433)	0,640 (0,517;0,923)	6,782 (5,786;12,552)
Patients with poor oral hygiene (n=12)	22,000 (17,050;26,950)	21,875 (9,000;30,750)	1,113 (2,063;2,588)	0,905 (0,667;1,033)	0,575 (0,489;0,832)	8,569 (5,595;12,695)
Kruskal-Wallis test	p=0,158	p=0,18	p=0,215	p=0,08	p=0,15	p=0,13

The Spearman rank correlation test allowed us to analyze the presence of correlations between the obtained data in each of the studied groups.

The assessment of correlations in each group was carried out using a series of Spearman rank correlation tests. In the group of patients with an excellent level of individual oral hygiene, no statistically significant correlations between the indicators were found. In the group of patients with a good level of hygiene, the following correlations were obtained according to the RNR: a weak direct correlation between the values of acid and alkaline phosphatase ($r = 0.375$, $p < 0.05$), a high-strength inverse correlation between the concentration of acid phosphatase in the oral fluid and the value of the mineralization index ($r = -0.799$, $p < 0.05$), as well as a direct medium correlation between IgA and IgM titers ($r = 0.563$, $p < 0.05$). In patients with a satisfactory level of personal hygiene, the following correlations were

observed: a direct weak correlation between the levels of acid and alkaline phosphatase in oral fluid ($r = 0.428$, $p < 0.05$), a direct weak correlation between the Ig G titer and the level of alkaline phosphatase ($r = 0.331$, $p < 0.05$), and an inverse high-strength correlation between the level of acid phosphatase and the value of the mineralization index ($r = -0.718$, $p < 0.05$). Patients with poor oral hygiene demonstrated the following correlations: a high-strength inverse relationship between the level of acid phosphatase and the mineralization index ($r = -0.811$, $p < 0.05$) and a direct medium relationship between the level of acid phosphatase and the concentration of IgG in oral fluid ($r = 0.643$, $p < 0.05$).

The last task of the research was to study the influence of the level of gingival inflammation on the parameters of oral fluid. In this study, we did not find any statistically significant differences in the titers of acid and alkaline phosphatase, the values of the mineralization

index and basic immunoglobulins in children and adolescents with JIA who had mild or moderate gingivitis

(ranking was carried out according to the value of the PMA index) (Table 5).

Table 5. Immunological profile of oral fluid and main biochemical markers of bone tissue activity depending on the degree of gingival inflammation in patients with JIA

	JIA patients with mild gingivitis (n = 52)	JIA patients with moderate gingivitis (n = 28)	p UMV
Alkaline phosphatase U/L	17,600 (14,300;25,300)	16,500 (13,700;23,700)	0,42
Acid phosphatase U/L	13,500 (6,000;26,250)	8,750 (6,125;23,065)	0,58
Mineralization index, c.u.	1,772 (0,951;2,713)	1,848 (0,992;2,951)	0,65
Ig A, g/L	0,910 (0,715;1,424)	0,920 (0,718;1,259)	0,68
Ig M, g/L	0,610 (0,496;0,828)	0,570 (0,442;0,867)	0,62
Ig G, g/L	7,108 (5,399;11,554)	6,589 (4,894;11,776)	0,45

The assessment of the correlations existing in the studied groups was carried out using a series of Spearman rank correlation tests. In the group of patients with mild gingivitis, the following correlations were found: a direct relationship of medium strength between the values of acid and alkaline phosphatases ($r = 0.59$, $p < 0.05$), an inverse high correlation between the concentration of acid phosphatase in oral fluid and the value of the mineralization index ($r = -0.735$, $p < 0.05$) and a direct weak correlation between IgA and IgM titers ($r = 0.31$, $p < 0.05$). The group of patients with JIA who had moderate gingivitis demonstrated the following correlations: direct relationships of weak strength between the concentrations of alkaline phosphatase and IgG ($r = 0.44$, $p < 0.05$), acid phosphatase and IgG ($r = 0.42$, $p < 0.05$) and IgG and IgM titers ($r = 0.411$, $p < 0.05$); also in this group there was a high-strength inverse relationship between the level of acid phosphatase and the value of the mineralization index.

DISCUSSION

The obtained data on statistically significantly increased levels of IgG in patients with juvenile idiopathic arthritis are partially consistent with the results of the study by Riis J.L. *et al.* (2020) [8], which indicated that high titers of this marker are associated with worsening dental status. At the same time, the variability of the studied immunoglobulin does not correlate with either indicators of systemic inflammation or with the total level of IgG. All this determines the relevance of further scientific studies aimed at studying the features of the course of dental diseases in patients with JIA.

The results obtained by us, indicating the absence of differences in IgA levels in the oral fluid of patients with JIA compared with adolescents without comorbidities, don't correlate with the data of Feres de Melo A.R. *et al.* (2014) [9]. In particular, the authors found a statistically significant decrease in sIgA levels relative to the control group; however, their study examined younger children, 6-12 years old.

Practical significance

The identified patterns contribute to the expansion of existing knowledge on the course of inflammatory

periodontal diseases in the context of JIA and may serve as a basis for developing targeted dental prevention programs for this patient group.

Study limitations

The limitations of this study are due to the peculiarities of its design, since the possible mutual influence of the above distribution factors was not taken into account when stratifying patients by subtype of the underlying disease and the nature of drug therapy.

Prospects for further research

Conducting multicenter prospective cohort studies on the relevant topic in Ukraine will allow us to confirm or refute the hypotheses formulated by us and will contribute to the deepening of scientific knowledge about the peculiarities of the course of inflammatory periodontal diseases in children with rheumatological pathology, in particular, juvenile idiopathic arthritis.

CONCLUSIONS

1. The fact of the presence of JIA in the patient, the subtype of the disease and its basic medical support in this study did not affect the levels of alkaline and acid phosphatase, the value of the mineralization index and the levels of IgA and IgM in the studied groups; however, we found patterns regarding IgG. Thus, patients with JIA have statistically significantly higher IgG titers compared to children in the control group. Patients undergoing treatment with MTX ≤ 15 mg demonstrate, on average, 1.57 times higher IgG titers compared to the indicators of the control group, with adalimumab – 1.6 times higher IgG titers. Patients with the oligoarticular variant have 1.8 times higher titers of the specified immunoglobulin compared to the control group.
2. In this study, we did not find any differences between the titers of acid and alkaline phosphatase, basic immunoglobulins and mineralization index values depending on the level of individual oral hygiene of patients with JIA.
3. The level of gingivitis in patients with JIA does not affect the concentration of the above-mentioned oral fluid indicators.

4. The obtained results indicate the feasibility and relevance of creating a comprehensive preventive program aimed at precluding periodontal tissue diseases in this category of patients.

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CONFLICT OF INTEREST

The authors note the absence of a conflict of interest at the stages of preparation and writing of the manuscript of the article.

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Активність ферментів-маркерів ремоделювання тканин пародонту та імунологічний профіль ротової рідини у пацієнтів підліткового віку, що хворіють на ювенільний ідіопатичний артрит

Актуальність. Вивчення особливостей ротової рідини пацієнтів із запальними захворюваннями пародонта на тлі ЮІА може сприяти пошуку діагностичних маркерів-предикторів важких форм даної стоматологічної нозології.

Ціль: визначити рівні кислоти та лужної фосфатази, імуноглобулінів класу А, М та G у ротовій рідині та значення індексу мінералізації у дітей підліткового віку, що хворіють на ЮІА, в залежності від базового медикаментозного супроводу захворювання, субтипу ЮІА, стану індивідуальної гігієни ротової порожнини та інтенсивності запалення ясен.

Матеріали та методи. У дослідження були включені 80 дітей віком від 10 до 17 років з ЮІА та 20 дітей-підлітків без супутньої патології. Кожному з учасників проведено базове стоматологічне обстеження з профарбовуванням зубних нашарувань, оцінка інтенсивності запалення індексом РМА та забір ротової рідини для визначення активності кислоти та лужної фосфатази, індексу мінералізації та титрів Ig А, М та G. Розподіл учасників відбувався п'ять разів: відповідно наявності ЮІА, базового медикаментозного супроводу (хворі, у схемі лікування яких використовуються метотрексат (MTX) у дозуванні ≤ 15 мг ($n = 43$), більшому за 15 мг ($n = 18$) або комбінація MTX та адаліумаб ($n = 19$)) та група контролю ($n = 20$), варіанті перебігу ЮІА (поліартикулярний РФ+ ($n = 29$) та РФ- ($n = 10$), недиференційований ($n = 5$), олігоартикулярний ($n = 24$), ентезит-асоційований ($n = 12$) та група порівняння ($n = 20$)), рівні індивідуальної гігієни на основі індексу РНР (відмінний ($n = 3$), хороший ($n = 28$), задовільний ($n = 37$) та поганий ($n = 12$)) та ступеня запалення ясен відповідно до значення індексу РМА (гінгівіт легкого ($n = 52$) та середнього ступеня ($n = 28$)) (останні два розподіли були проведені у межах пацієнтів із ЮІА).

Результати. Факт наявності ЮІА, його субтип та медикаментозний супровід не впливають на активність кислоти та лужної фосфатази, значення індексу мінералізації, титри IgА таМ, проте чинять вплив на титр IgG: пацієнти з ЮІА, які проходять лікування з використанням MTX ≤ 15 мг та адаліумабом та пацієнти з олігоартикулярним ЮІА мають вищі титри даного імуноглобуліну в порівнянні з групою контролю у 1.57, 1.6 та 1.8 рази відповідно. Нами не було виявлено впливу ступеня запалення ясен та стану індивідуальної гігієни у пацієнтів із ЮІА на аналізовані показники.

Висновки. Дві виявлені закономірності сприяють розширенню наявних знань щодо перебігу запальних захворювань пародонта на тлі ЮІА та можуть бути покладені в основу розробки таргетних програм стоматологічної профілактики для даної групи пацієнтів.

Ключові слова: підлітки, ротова рідина, артрит ідіопатичний, кисла фосфатаза, лужна фосфатаза, імуноглобулін.