Recieved: 23 April 2015/ Accepted: 27 May 2015/ Published online: 15 June 2015

Prevalence of Connective Tissue Dysplasia Signs in Patients with Rheumatoid Arthritis and Characteristics of Comorbidity Course

Roman O. Demidov [1] ; http://orcid.org/0000-0002-5260-1719
E-mail: demid_333@mail.ru

Svetlana A. Lapshina [1] ; http://orcid.org/0000-0001-5474-8565

[1] Department of Hospital Therapy, Kazan State Medical University, Kazan, Republic of Tatarstan, Russian Federation

ABSTRACT

BACKGROUND

Genetic predisposition and congenital disorders of musculoskeletal system play major role in the development of rheumatoid arthritis (RA). Risk of RA development is associated with the major histocompatibility complex class II antigen HLA-DR4. Patients with connective tissue dysplasia (CTD) have increased predisposition to development of rheumatoid arthritis due to similarities in pathogenesis and presence of HLA system antigens. As for the moment the issue of RA course characteristics is not yet properly investigated and is open for further discussion.

METHODS

Among 107 patients with RA, observed in rheumatology departments of Republican Clinical Hospital and City Clinical Hospital №7 in Kazan, 18 (16.8%) patients (15 females and 3 males) with reliable signs of CTD were selected. The average age of cases was 47.9 ± 12.89 years. Duration of illness was 9.94 ± 5.59 years. Positive RF was in 17 (94.4%) patients. According to DAS28, low disease activity was identified in 1 (5.6%) patient, moderate - in 13 (72.2%), high - in 4 (22.2%). During the course of this study clinical status of patients, laboratory (ESR, CRP, RF) and instrumental (joints x-ray, electrocardiography, echocardiography, densitometry) parameters were evaluated.

RESULTS

The most common signs of CTD among the patients were: VVD - in 14 (77.7%), myopia - in 9 (50%), mitral valve prolapse (MVP) - in 6 (33.3%), small heart abnormalities - in 8 (44.4%), flatfoot - in 6 (33%), scoliosis - in 5 (27,7%), hyperkyphosis - in 2 (11.1%), joint hypermobility - in 2 (11.1%), structural abnormalities of the kidneys - in 2 (11.1%), rhythm and conduction disorders - in 7 (38.8%), asthenic syndrome - in 11 (61.1%), chronic tonsillitis - in 5 (27.7%), cardiac sphincter insufficiency - in 3 (16.6%), hemorrhoids - in 1 (5.5%), bronchiectasis - in 1 (5.5%). There were the following two groups of patients: first one (n=9) from 1 to 5 and second one (n=9) - 6-9 signs of dysplasia. Differences in RA activity were acquired depending on the presence of myopia (DAS28= 4.68±0.87, CRP= 24.89±8.17 mg/l, ESR 34.88±13.51 mm/h, duration of illness 12.77±6.03 years, radiologic stage 3.22±0.66) or its absence (DAS28=3.78±1.06, CRP=16.86±14.16 mg/l, ESR 22.87±7.54 mm/h, duration 6.75±2.81 years, radiologic stage 2.87±0.83); flatfoot (DAS28=4.53±1.05, CRP=27.58±5.88 mg/l, ESR 37.5±14.65 mm/h, radiologic stage 3.33±0.81, duration of illness 12.33±6.97 years) or its absence (DAS28=4.04±1.02, CRP=17.65±12.69 mg/l, ESR 24.72±8.74 mm/h, radiologic stage 2.9±0.70, duration of illness 8.63±4.52 years).

CONCLUSION

Among the patients with RA signs of CTD appear with a higher frequency than in population (16.8% towards 10%). Myopia, VVD, heart pathology and osteoporosis were the most frequent.

KEYWORDS

Connective tissue, Collagen, Joint Hypermobility, Osteoporosis, Osteoarthritis

INTRODUCTION

Rheumatoid arthritis (RA) - is a chronic systemic immune-mediated disease of connective tissue, characterised by persistent inflammation predominantly of peripheral joints with development of symmetric progressive erosive and destructive polyarthritis [1, 2]. Complexity of mechanisms of RA development and its expressed clinical polymorphism are caused by interaction of external and internal environmental factors genetically determined and acquired defects of immune regulation. There is an ongoing discussion about the viral (e.g., Epstein-Barr virus, cytomegalovirus, herpes viruses, rubella) and bacterial (e.g., Proteus mirabilis and others) infections that can act as triggers to the disease. This is so-called "molecular mimicry" hypothesis, according to which antigens of disease-causing agents can trigger an autoimmune process due to similarities in peptide sequence between the structure of microorganism and tissues of the host [3]. Different toxic (components of tobacco and mineral oils), endogenous (collagen types II, IX, X, XI, proteoglycans, citrullinated proteins) and nonspecific (allergens, psycho-emotional stresses) factors can act as "arthrogenic". Detection of rheumatoid factor (RF) and anti-citrullinated

protein antibody (ACPA) in human serum a few years before the first RA symptoms appear indicates changed immunologic status of these individuals: apparently, genetic predisposition (e.g., HLA system alleles) and triggers (e.g., long-term smoking) may cause immunopathological shift in human organism and determine development of RA [4, 5]. In 2004 Dutch and Swedish scientists discovered an expressed correlation between carriage of SE (shared epitope) and detection of ACPA [6, 7].

In recent years, more attention is attracted to a role of different diseases of human organs and systems that are associated with connective tissue dysplasia (CTD). Significance of this problem is caused by widespread of CTD, systemic character of affections, high probability of development of different types of pathology. Moreover, this condition can not only decrease the quality of life and influence the course of intercurrent diseases, but also predict a poor prognosis.

In 1988, P. Beighton introduced the term «connective tissue dysplasia» [8]. In Russian Federation, it was acknowledged in 1990 at the CTD conference in Omsk [9]. Connective tissue dysplasia is a pathological condition, caused by genetically determined connective tissue development defect that occurs in fetal and postnatal periods, leads to dysfunction of organs and tissues, has a progredient course, its morphological base are the defects of collagen structure that cause fiber structures and ground substance alteration [10,11]. Morphological alterations in organs and tissues are unspecific and manifest identically in different types of dysplasia, while having various severity. Genetic defects of various connective tissue components define the reduction of its stability and solidity, lead to the formation of clinical manifestations in those organs and tissues where presence of connective tissue is maximal. CTD is associated with the mutation of extracellular matrix protein (collagen types IV-VII), and increased histocompatibility antigens (HLA-28, B 35, B 27, A 1, DR 6, CW5, CW 52) presentation is identified on leucocytes membrane [12]. Influence of environment plays a role of a trigger. Clinical manifestations will depend on the type of predominantly involved connective tissue (loose or dense), quality and quantity of mutations, nature and severity of fibrillogenesis defect. Since connective tissue spreads equally all over the body, (it is present in bones, skin, cartilage, vessel wall, stroma of organs) the disease is polysistemic and has various symptoms [13].

Presence of HLA system antigens and similarities in pathogenesis determine higher predisposition to RA development in patients with CTD. There are various course characteristics of rheumatoid diseases depending on the congenital connective tissue pathology. Evidence of clinical connection between CTD and osteoarthritis (OA) suggests that OA develops more frequently in patients with connective tissue dysplasia and its severity correlates with quantity of phenotypic signs of CTD [14]. Joint hypermobility (JHM) affects the incidence and severity of OA in the same way [15, 16]. CTD markers occur with high frequency among patients with osteoarthrosis. If high amount of CTD signs is present, osteoarthrosis manifestation will be seen at the young age. Inflammation promotes the development of secondary osteoarthrosis in patients with RA, including major joints [17]. Therefore, combination of CTD and RA can affect the rate of osteoarthrosis development in a negative way and lead to a rapid limitation of joint function, decreasing life quality of a young patient.

The aim of this study was to investigate the prevalence CTD signs in patients with RA and to analyse characteristics of RA course in patients with connective tissue dysplasia.

METHODS

In accordance with the aim, 107 patients with RA observed in rheumatologic departments of RCH and CCH №7 in Kazan were included in the study from October 2014 until February 2015. 18 (16.8%) patients were selected with reliable signs of CTD. Clinical characteristic of patients included in the study is presented in Table 1.

Patients underwent routine clinical examination, number of swollen and painful joints was estimated, and complete physical examination was conducted. Study of disease anamnesis was performed by surveying and questioning the patients, medical documentation was used. Results were recorded into specially developed research card.

Parameters	n	%
Mean age	47.9±12.89 years	
Gender, f/m	15/3	
Duration of illness	9.94±5.59 years	
Positive RF	17	94.4 %
Disease activity		
1 = low (DAS28 2.6-3.2)	1	56.6 %
2 = moderate (DAS28 3.3-5.1)	13	72.2 %
3 = high (DAS28 > 5.1)	4	22.2 %
Radiologic stage (by Steinbrocker)		
Stage II	4	22.3 %
Stage III	8	44.4 %
Stage IV	6	33.3 %

Table 1. Characteristic of patients with rheumatoid arthritis with signs of CTD that were included in the study

All patients underwent CBC with differential and a standard biochemical blood analysis upon admission. Also measured the concentrations of C-reactive protein (CRP), rheumatoid factor (RF).

During the course of study, instrumental (joint X-ray, electrocardiography, echocardiography, and densitometry) parameters were evaluated. Standardised scales for pain (visual analogue scale - VAS), disease activity, visual acuity, VVD evaluation were used. Joint hypermobility was evaluated according to Beighton modification of the Carter - Wilkinson scoring system. Diagnosis of scoliosis was determined by Adam's test and by radiography with measurement of Cobb angle. Diagnosis of flatfoot was determined using Friedland method. A questionnaire on the presence of CTD symptoms developed by us was used.

Statistical analysis was compiled through application package STATISTICA 6.0 (StatSoft, USA). Data in the descriptive statistics are presented in the form of M±SD, with M being the average value of the attribute and SD being mean square (standard) deviation. The correlation analysis was used.

RESULTS

Findings on the prevalence of connective tissue dysplasia are few and contradictory, due to the various classification and diagnostic approaches used by the authors. One of the few works by V.O Dedova, N.Ya. Dotsenko et al., presents data on the prevalence of CTD in the population depending on the frequency of symptoms in the population [18].

In most (57-94%) cases CTD is diagnosed by existing pathology of the skeleton: deformation of the chest and spine, flatfoot, joint hypermobility.

Pathology of the muscular system is characterised by hypotrophy (47%), muscle hypotonia (33%), diastasis recti abdominis (31%), abdominal hernias (3-19.5%); pathology of the skin - in the form of skin hyperelasticity (13-50%), striae (8%). Among the lesions of cardiovascular system the most common (3-10%) are mitral valve prolapse and false chord of the left ventricle. Pathology of the circulatory system typically manifests in the form of varicose illness (6-23.5%) and hemorrhoids (40%). Ophthalmologic manifestations of varying degrees like myopia (38%), astigmatism (17%), dislocation and subluxation of the lens (12%) occurs in more than one-third of patients with CTD. Pathology of the gastrointestinal tract can often be present as disorders of motor function (19,2%), anomalies of the gallbladder (35%), biliary dyskinesia (11%), gastroptosis (10%). In the urinary system CTD often appears in the form of nephroptosis - 9.1 - 20% of cases, structural abnormalities of the kidneys - in 11.6%. Involvement of bronchopulmonary system (6%) is quite rarely observed. Involvement of nervous system can be characterized by a vegetative-vascular dystonia syndrome - in 68-87% of cases, cerebrovascular disorders syndrome (mainly migraine-type headaches – 19.7-50.4%), mental disorders syndrome (emotional lability, and others) [18].

The prevalence of CTD in patients with RA in Kazan and the Republic of Tatarstan was studied by identifying specific symptoms and was equal to 16.8% (n = 18) among patients with RA (n = 107). The following signs of CTD (Table 2) were most common in studied patients.

Structural abnormalities of the kidneys were present in 2 (11.1%), asthenic syndrome - in 11 (61.1%), chronic tonsillitis - in 5 (27.7%) patients.

Osteoporosis was present in 11 (61.1%) patients. Such common signs of CTD as pathology of skin and muscular system were not present among the observed patients with RA.

The number of signs of dysplasia ranged from 1 to 9 in a single patient. Typically there were 4 - 6 signs in a single patient (Diagram 1).

There were the following two groups of patients: first one (n=9) from 1 to 5 and second one (n=9) - 6-9 signs of dysplasia.

There was a significantly ($p \leq 0.05$) higher DAS28 (4.52±1.20), CRP (24.79±9.25 mg/l) activity in the second group (age 46.75±15 years, radiologic stage 3.25±0.70) compared with the first one (DAS28=3.95±0.81, CRP=7.96±13.13 mg/l, age 49±11.32 years, radiological stage 2.88±0.78) (Diagram 2).

Signs of CTD	In general in population [18]	Among patients with RA (n=18)
Vegetative-vascular dystonia syndrome	68-87 %	77.7% (n=14)
Myopia	38%	50% (n=9)
Mitral valve prolapse (MVP)	3-10%	33.3% (n=6)
Flatfoot	60.5 - 78%	33.3% (n=6)
Scoliosis	70 - 80%	27.7% (n=5)
Hyperkyphosis	11-19%	11.1% (n=2)
Joint hypermobility	25 - 33 %	11.1% (n=2)
Rhythm and conduction disorders	6.5%	38.8% (n=7)
Hemorrhoids	40%	5.5% (n=1)
Disorders of motor function	19.2%	16.6% (n=3)
Structural abnormalities of the kidneys	11.6%	11.1% (n=2)
Involvement of bronchopulmonary system	6%	5.5% (n=1)

Table 2. Prevalence of connective tissue dysplasia signs in population and in patients with RA

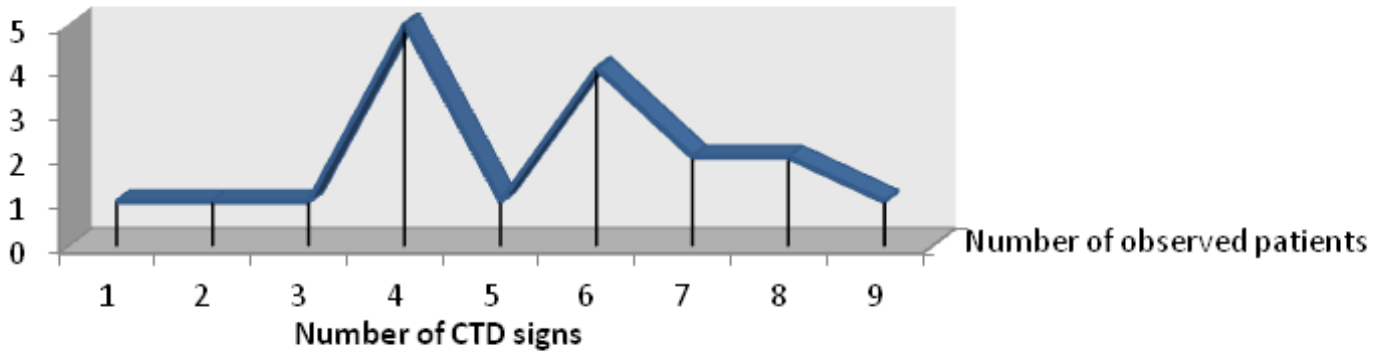

Diagram 1. Number of CTD signs in patients with RA

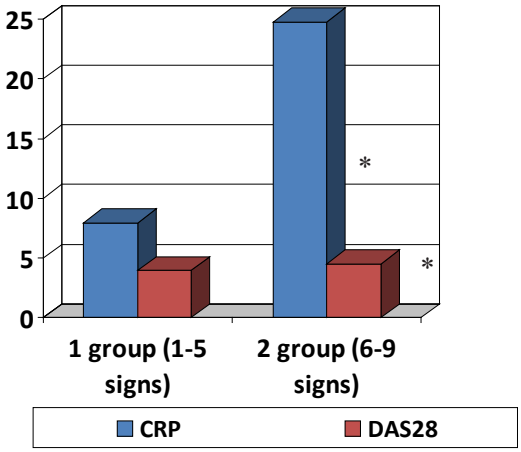

Diagram 2. Characteristic of patients divided into groups by the number of signs (for more explanation, see the main text).

**- significance (p≤0.05) of differences of parameters in patient groups depending on the number of signs.*

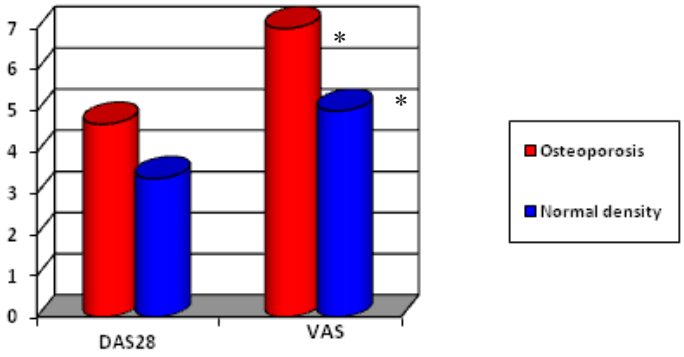

Diagram 3. Characteristic of patients according to activity (DAS28) and pain intensity by VAS scale depending on the presence of osteoporosis and normal mineral bone density respectively (for explanation, see the main text).

**- significance (p≤0.05) of parameters differences in patient groups depending on the presence or absence of osteoporosis.*

Signs	DAS28	CRP (mg/l)	ESR (mm/h)	Duration of illness (years)	Radiologic stage
Myopia	4.68±0.87*	24.89±8.17*	34.88±13.51*	12.77±6.03*	3.22±0.66
Absence of myopia	3.78±1.06	16.86±14.16	22,87±7.54	6.75±2.81	2.87±0.83
Flatfoot	4.53±1.05	27.58±5.88**	37.5±14.65**	12.33±6.97**	3.33±0.81
Absence of flatfoot	4.04±1.02	17.65±12.69	24.72±8.74	8.63±4.52	2.9±0.70

Table 3. Characteristic of patients according to RA activity depending on the presence of myopia and flatfoot.

**- significance (p≤0.05) of parameters differences in patient groups depending on the presence or absence of myopia.*
***- significance (p≤0.05) of parameters differences in patient groups depending on the presence or absence of flatfoot.*

Differences in RA activity depending on the presence or absence of myopia and flatfoot were acquired (table 3).

Significant (p≤0.05) difference was identified in patients with osteoporosis in terms of activity (DAS28=4.68±0.97), pain intensity according to VAS (6.90±1.44 sm), compared with patients with normal bone tissue density (DAS28=3.36±0.36, pain VAS=5.83±2.22 sm).

DISCUSSION AND CONCLUSION

Among patients with RA signs of connective tissue dysplasia appear with higher frequency than in the population (16.8% towards 10%).Myopia, vegetative-vascular dystonia, pathology of the heart (small heart abnormalities: patent foramen ovale, false tendons of left ventricle; mitral valve prolapse; rhythm and conduction disturbances) were most frequent. In general, the distribution of certain features of connective tissue dysplasia was different from that of the population. Thus kyphoscoliosis, flatfoot, joint hypermobility, varicose illness, hemorrhoids, skin hyperelasticity, hypotrophy were the most common in the population. Such widespread signs as joint hypermobility, skin and muscular system lesions were practically absent in our patients. On the other hand, myopia and MVP were much more frequent. We assume that the sample of patients is small but nevertheless identified trends require further study. Similar studies are not found in available literature and the findings about the prevalence of dysplasia in a population are few. Patients with signs of dysplasia had a tendency towards higher activity of RA that accordingly leads to a faster disease progression. Osteoporosis was commonly present in patients,

but it is difficult to determine what the cause of its development was: connective tissue dysplasia or rheumatoid arthritis, as well as its therapy (glucocorticoids). It is known that both diseases have a negative impact on the decrease in the bone mineral density [19, 20]. Therefore, the combination of the two pathologies may increase the risk of osteoporotic fractures. Thus, the prevalence of osteoporosis was 61.1% in the examined patients, in patients with RA 10-67% [21-24], in patients with connective tissue dysplasia 28.7% [25]. With the increase of CTD signs over 5, RA activity and the severity of pain increase significantly.

Therefore, rapid progression of the disease and limited joint mobility can be assumed in the presence of connective tissue dysplasia markers in patients with RA. It is therefore necessary to consider this during patient examination and therapy appointment.

ACKNOWLEDGEMENTS

None

REFERENCES

1. Mohan VK, Ganesan N, Gopalakrishnan R. Association of susceptible genetic markers and autoantibodies in rheumatoid arthritis. J Genet. 2014;93 (2): 597-605.

2. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH,Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Ménard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovský J, Wolfe F, Hawker G. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborativeinitiative. Arthritis Rheum. 2010; 62 (9): 2569-2581.

3. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011; 365 (23): 2205-2219.

4. van der Helm-van Mil AH, Verpoort KN, le Cessie S, Huizinga TW, de Vries RR, Toes RE. The HLA-DRB1 shared epitope alleles differ in the interaction with smoking and predisposition to antibodies to cyclic citrullinated peptide. Arthritis Rheum. 2007; 56 (2): 425-432.

5. Kallberg H, Padyukov L, Plenge RM, Ronnelid J, Gregersen PK, van der Helm-van Mil AH, Toes RE, Huizinga TW, Klareskog L, Alfredsson L; Epidemiological Investigation of Rheumatoid Arthritis study group. Gene-gene and gene-environment interactions involving HLA-DRB1, PTPN22, and smoking in two subsets of rheumatoid arthritis. Am J Hum Genet. 2007;80 (5): 867-875.

6. Berglin E, Padyukov L, Sundin U, Hallmans G, Stenlund H, Van Venrooij WJ, Klareskog L, Dahlqvist SR. A combination of autoantibodies to cyclic citrullinated peptide (CCP) and HLA-DRB1 locus antigens is strongly associated with future onset of rheumatoid arthritis. Arthritis Res Ther. 2004; 6 (4): R303-308.

7. van Gaalen FA, van Aken J, Huizinga TW, Schreuder GM, Breedveld FC, Zanelli E, van Venrooij WJ, Verweij CL, Toes RE, de Vries RR. Association between HLA class II genes and autoantibodies to cyclic citrullinated peptides (CCPs) influences the severity of rheumatoid arthritis. Arthritis Rheum. 2004; 50 (7): 2113-2121.

8. Beighton P, de Paepe A, Danks D, Finidori G, Gedde-Dahl T, Goodman R, Hall JG, Hollister DW, Horton W, McKusick VA, et al. International Nosology of Heritable Disorders of Connective Tissue, Berlin, 1986. Am J Med Genet. 1988;29 (3): 581-594.

9. Yakovlev VM. Terminologiya, opredeleniya s pozitsiy kliniki, klassifikatsiya vrozhdyonnoy displazii soedinitelnoy tkani (Terminology, definitions from the standpoint of the clinic, the classification of congenital connective tissue dysplasia). Congenital connective tissue dysplasia: abstracts of the symposium. 1990, pp 3-5.

10. Alunno A, Manetti M, Caterbi S, Ibba-Manneschi L, Bistoni O, Bartoloni E, Valentini V, Terenzi R, Gerli R. Altered Immunoregulation in Rheumatoid Arthritis: The Role of Regulatory T Cells and Proinflammatory Th17 Cells and Therapeutic Implications. Mediators Inflamm. 2015;2015:751793.

11. Nechaeva GI, Yakovlev VM, Konev VP. Displaziya soedinitelnoy tkani: osnovnyie klinicheskie sindromyi, formulirovka diagnoza, lechenie (Connective tissue dysplasia: the major clinical syndromes, formulation

of diagnosis, treatment). The Practitioner Medical Journal. 2008; 2: 22-28.

12. Furukawa H, Oka S, Shimada K, Hashimoto A, Tohma S. Human leukocyte antigen polymorphisms and personalized medicine for rheumatoid arthritis. J Hum Genet. 2015 Apr 23.

13. Malysheva O, Bedrich A, Kuipers JG, Kleine H, Wolff B, Baerwald CG. Use of clinical scores to guide therapeutic decisions in patients with rheumatoid arthritis in daily care. Clin Exp Rheumatol. 2015; 33 (2): 255-258.

14. van Heemst J, van der Woude D, Huizinga TW, Toes RE. HLA and rheumatoid arthritis: how do they connect? Ann Med. 2014;46 (5): 304-310.

15. Chen HC. Inverse Association of General Joint Hypermobility With Hand and Knee Osteoarthritis and Serum Cartilage Oligomeric Matrix Protein Levels. Arthrit Rheum. 2008; 58 (12): 3854-3864.

16. Pacey V, Nicholson LL, Adams RD, Munn J, Munns CF. Generalized joint hypermobility and risk of lower limb joint injury during sport: a systematic review with meta-analysis. Am J Sports Med. 2010; 38 (7): 1487-1497.

17. Goodman SM. Rheumatoid arthritis: Perioperative management of biologics and DMARDs. Semin Arthritis Rheum. 2015 Jan 30.

18. March L, Smith EU, Hoy DG, Cross MJ, Sanchez-Riera L, Blyth F, Buchbinder R, Vos T, Woolf AD. Burden of disability due to musculoskeletal (MSK) disorders. Best Pract Res Clin Rheumatol. 2014; 28 (3): 353-366.

19. Khokhlova OI, Kalaeva GIu, Ust'iantseva IM. [Characteristics of the bone tissue metabolism in adolescents with the connective tissue's undifferentiated dysplasia] [Article in Russian]. Fiziol Cheloveka. 2014; 40 (3): 101-108.

20. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, Combe B, Cutolo M, de Wit M, Dougados M, Emery P, Gibofsky A, Gomez-Reino JJ, Haraoui B, Kalden J, Keystone EC, Kvien TK, McInnes I, Martin-Mola E, Montecucco C, Schoels M, van der Heijde D; T2T Expert Committee. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010; 69 (4): 631-637.

21. Oelzner P, Schwabe A, Lehmann G, Eidner T, Franke S, Wolf G, Hein G.

Rheumatol Int. Significance of risk factors for osteoporosis is dependent on gender and menopause in rheumatoid arthritis. 2008; 28 (11):1143-1150.

22. Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK. Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County Rheumatoid Arthritis register. Arthritis Rheum. 2000;43 (3): 522-530.

23. Ørstavik RE, Haugeberg G, Mowinckel P, Høiseth A, Uhlig T, Falch JA, Halse JI, McCloskey E, Kvien TK. Vertebral deformities in rheumatoid arthritis: a comparison with population-based controls. Arch Intern Med. 2004; 164 (4): 420-425.

24. Trieb K. Arthrodesis of the wrist in rheumatoid arthritis. World J Orthop. 2014; 5 (4): 512-5.

25. Supine MI, Nechaeva GI. Profilaktika narusheniy mineralnoy plotnosti kosti u podrostkov s displaziey soedinitelnoy tkani (Prevention of abnormality of bone mineral density with teenagers with connenctive tissue dysplasia). The Practitioner Medical Journal. 2014; 4: 38-40.