

Received: 2015.07.02
Accepted: 2016.02.04
Published: 2016.03.04

Metabolism of glycosaminoglycans in the course of juvenile idiopathic arthritis*

Metabolism glikozoaminoglikanów w przebiegu młodzieńczego idiopatycznego zapalenia stawów

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Summary

Juvenile idiopathic arthritis (JIA) is a non-homogeneous autoimmune children's disease which, despite the applied therapy, has a progressive character with recurrences, leading to damage of joint structures. Progressive wearing of the joint cartilage in the course of JIA, which results from the imbalance between the biological strength of the cartilage, its function and exerted pressure forces, is linked to metabolic disorders of extracellular matrix (ECM) components. Among the latter compounds, the proteoglycan (PG) aggrecan plays a particular role in maintaining the mechanical-immunological properties of the cartilage. These functions are directly related to chains of glycosaminoglycans (GAGs), covalently linked to the core protein of PGs. Therefore, every change of GAGs metabolism linked to an increase of the rate of degradation or with a decrease of their biosynthesis may have pathological consequences.

In this paper we aim to describe plausible mechanisms leading to observed disorders of aggrecan transformation in children, which are reflected in the profile of plasma GAGs. Therefore, we describe the plausible role of factors related to catabolism and synthesis of PGs/GAGs as well as the contribution of immunological processes to shaping the changes of extracellular matrix components in the course of JIA.

Keywords: juvenile idiopathic arthritis • glycosaminoglycan • aggrecan • extracellular matrix remodeling

Full-text PDF: <http://www.phmd.pl/fulltxt.php?ICID=1196355>

Word count: 3661

Tables: –

Figures: –

References: 95

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of autoimmune joint disorders leading to the degeneration of osteoarticular structures, muscle atrophy and growth disturbance, which, in turn, results in the sick child's disability. It is said that the arthritis-indicating symptoms, which persist for at least six weeks in children before reaching 16 years of age, constitute the basis for diagnosing JIA [31,34,68]. However, other disease entities progressing with joint structure inflammation, including infectious, reactive, allergic and toxic arthritis as well as atrophies occurring in the course of auto-immune diseases, cancers, blood diseases, metabolic conditions and non-inflammatory connective tissue disease, fibromyalgia and psychogenic gout should be excluded [31,33,68]. Having taken into account the complexity and non-homogeneity of the clinical picture of the disease, which was observed during the mentioned 6 weeks of the disorders, and distinctiveness in the laboratory results of diagnostic tests, the International League of Associations for Rheumatology (ILAR) distinguished seven subtypes of JIA: systemic JIA, oligoarticular JIA, rheumatoid factor (RF)-negative polyarticular JIA, RF-positive polyarticular JIA, enthesitis-related arthritis, psoriatic arthritis and undifferentiated JIA [31,33,34,62,68,81].

Juvenile idiopathic arthritis is the most frequent, chronic, inflammatory disease of the connective tissue in children. The incidence of JIA is estimated at 2 to 20 cases per 100,000 children, with a prevalence of 16 to 150 cases per 100,000 children worldwide, with no clear racial predilection [33,68]. The disease rarely occurs in children before 6 months of age. However, it is not uncommon to discover a family history of autoimmune disease. Similarly to most rheumatic disease, JIA occurs more often in girls than in boys [31,33,54,67]. Apart from the direct stimulating influence of estrogens, it is supposed that the factor which predisposes females to JIA development, especially with oligoarthritic or polyarthritic onset, is the directed inactivation of one of two X chromosomes (father's or mother's) occurring in gametes during early stages of development. Moreover, it is assumed that in the case of girls with visible JIA, the process of inactivation of the X chromosome is inappropriate, i.e. disproportionate. Therefore, the majority of cells (>75%) inactivated the same X chromosome, while the rest inactivated the second chromosome. As a result, in girls with the mentioned defect, the antigens encoded by genes on the X chromosome, originating from a minority of cells, may not be presented to thymocytes in the thymus and do not elicit immune tolerance for them. As a consequence, these antigens are recognized as foreign bodies and stimulate the autoimmune response [16,40,42,54,82].

Variation in the incidence of JIA depends not only on the patient's sex but also on the environmental, ethnic and climate conditions [48,58,72].

Pathogenesis of JIA

The pathogenesis of JIA is complex and has not been fully explained yet. It is emphasized that the factor playing the most important role in the initiation of the inflammatory reaction, which is the basis for the pathology in question, is the genetic predisposition, which most frequently manifests itself under the influence of unfavorable external conditions including infection, stress or psychosocial factors in the broad sense [34,44,58,76]. Among all the enumerated external stimuli which influence the development of the pathology in question, the ones which are ascribed with the greatest importance are infectious agents, both viral, such as parvovirus B19, rubella virus, influenza virus or Epstein-Barr virus, and bacterial, including *Mycoplasma pneumoniae*, *Chlamydia trachomatis*, *Chlamydia/Chlamydophila pneumoniae*, *Borrelia burgdorferi*, *Yersinia enterocolitica*, *Proteus mirabilis* and *Streptococcus pyogenes* [5,7,18,27,31,34,41,44,63,66,68,69,78]. The hypothesis about the role of infectious agents in the pathogenesis of JIA is confirmed by the presence of antibodies recognizing bacterial heat shock proteins as well as lipid A of Gram-negative bacteria in the patient's blood. It is supposed that the fragments of bacterial peptidoglycans are transported to the joint by macrophages and dendritic cells, which induces subsequent links in the chain reaction of inflammation [5,51,58,79]. All the mentioned factors disturb correct metabolism of the immune system, which results in both production of autoantibodies and changes in the range of signal protein synthesis, cytokines and adhesion molecules.

JIA genetic predisposition

Juvenile idiopathic arthritis is not a genetically transmitted disease. However, human leukocyte antigens (HLA) contribute to its occurrence [40]. It is said that certain sets of HLA antigen molecules favor the autoimmune response and destructive changes in the motor system, leading to specific forms of JIA, while other antigens counteract the occurrence of arthropathy [2,30,64]. Therefore, a link between the presence of HLA antigens, including DRB1 with several different alleles (01, 04, 08, 11, 1103, 0401), DPB1 (02, 03), DQA1 (02, 03, 05), DQB1 (03, 04, 05), C, A2, B27 and DR4, and the development of arthropathy has been found [30,31,34,44,58,64,67,68,81]. Unlike the above-mentioned HLA antigens, which predispose to the development of JIA, the presence of the allele HLA-DRB1 (1501) is a factor which lowers the risk of the disease [2,3,30,64,65].

An increased risk of the autoimmune disease is also caused by polymorphism of genes not linked to the HLA system, the products of which regulate the course of the acquired immune response [2,24,58,64,73]. These products include cytokines and their receptors, signal peptides which initiate or block the immune reactions and protein receptors for lymphocytes. The mentioned genetic polymorphism occurs as a result of structural changes within the genome which may concern the sin-



gle nucleotide polymorphism (SNP) or the areas covering longer nucleotide sequences. It has been proven that about 100 SNPs, which are present in different genes, increase the risk of developing different types of JIA [48,64]. A particular role in the above-mentioned process is ascribed to SNP in the region of TRAF1/C5 on chromosome 9 [2,9,58]. Such polymorphism results in both transmittance disturbance, depending on tumor necrosis factor (TNF- α), and changes in the complement system [2,64,73]. Furthermore, a significant contribution to JIA development is made by SNPs within genes encoding different cytokines such as RANTES (regulated on activation, normal T-cell expressed and secreted), MIF (macrophage migration inhibitory factor), IL-1A (interleukin), IL-6 or IL-10 as well as PTPN22 (protein tyrosine phosphatase non-receptor type 22) or WISP3 (Wnt1-inducible signaling pathway protein 3) [2,24,31,58,64,65,95]. Among all the mentioned cytokines, only IL-10 has anti-inflammatory properties [94].

Proinflammatory factors in JIA pathogenesis

Proinflammatory factors, which are synthesized by monocytes or macrophages and neutrophils, are ascribed with a crucial role in generating the process of inflammation which leads to joint cartilage destruction both in children and adults [31,48,77,92,94]. Early stages of joint structures' destruction in the course of JIA are associated with excessive reactivity of T-cells towards their own antigens, very often constituted by extracellular matrix components which, in turn, build the osteoarticular structures [12,34,36,77,90,92]. These antigens include aggrecan, which is the major proteoglycan in cartilage, fibrin, a component of elastic fibers, and metalloproteinase 3 (MMP-3) peptides [39,90]. The mentioned antigens activate T-cells, stimulate their proliferation, and cause hypersecretion of proinflammatory cytokines. This results in imbalances between the concentration of proinflammatory factors, such as TNF- α , interferons γ (IFN- γ), interleukins including IL-1 β , IL-2, IL-6, IL-8, IL-12, IL-17 and IL-18, and the concentrations of such proinflammatory factors as IL4, IL-13, IL-10 and transforming growth factor β (TGF- β) [12,17,19,31,34,35,37,38,48,74,94]. Among all the mentioned compounds, TNF- α seems to play a special role in initiating the inflammatory process [17,19,35,37,38,48,74,80,94]. This factor, characterized by pleiotropic activity, enhances the influx of leukocytes into the synovial membrane, stimulates proliferation and differentiation of T-cells, induces collagenase synthesis in chondrocytes and osteoclast stimulation, and leads to joint cartilage destruction, synovial membrane outgrowth and resorption of the bone tissue [17,35,38,74,94]. Moreover, it stimulates monocytes and macrophages, which spurs the synthesis of further proinflammatory growth factors, cytokines and oxidative factors [17,38,74,94]. On the other hand, by enhancing the synthesis of prostaglandin E and IL-1 β , it leads to fevers occurring in children and, by strengthening the catabolic processes in muscle and adipose tissue, it contributes to weight gain or lower body weight in patients [35]. In the

pathogenesis and simultaneously in sustaining the inflammatory process in the course of JIA, a crucial role is played by IL-1 β , which enhances the chemotaxis of dendritic cells, macrophages and neutrophils and, moreover, induces the proliferation of fibroblasts and synoviocytes [17,35,94]. Furthermore, by influencing the patient's central nervous system, this interleukin is the cause of the patient's weakness and fever [19]. On the other hand, by activating the vascular endothelial cells, IL-1 β favors the occurrence of skin rashes, particularly in patients with a diagnosed disorder with polyarticular RF (+) [19,44]. Another pro-inflammatory factor in the cascade of the inflammatory process in question is IL-6, which stimulates hepatocytes to synthesize acute phase proteins and enhances chemotaxis of leukocytes [19,35,94]. What is more, IL-6, similarly to other previously mentioned factors, in the microenvironment within the joints of JIA patients favors the differentiation of precursor T cells toward Th17 cells rather than immunosuppressive Treg cells. The imbalance between autoreactive Th17 and Treg cells leads to the failure of T cell tolerance to self-antigens [19,44,80]. Moreover, IL-6 contributes to the development of anemia in children by inducing the liver to synthesize hepcidin, with subsequent restriction of plasma iron turnover [44,80].

Immunological factors in JIA pathogenesis

In the course of JIA, different kinds of disorders in the cell and humoral immunological response have been found. They are demonstrated, among others, by antibodies present in blood and in other body fluids [22,46,89]. The serological markers of the disease include the rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), antinuclear antibodies (ANA) and antibodies recognizing various antigens of the extracellular matrix which contribute to forming the osteoarticular structures [46,48,67,81,89]. The first mentioned marker, i.e. the rheumatoid factor type IgM, is the main serologic marker of rheumatoid arthritis in adults, while in children with JIA it is diagnosed only in about 20-30% of all cases. In the early stage of the disease, it is diagnosed even more rarely – in 5-10% of all cases [46,89]. It mainly occurs in children with the polyarticular type of the disease, while in general and oligoarthritic types of the disorder, the RF-IgM is detected sporadically. Moreover, in the blood of children with JIA, the presence of types of rheumatoid factors other than IgM, such as IgG, IgA or IgE, has been confirmed. It is suggested that the occurrence of RF in the pediatric patient's blood is linked to both severe course of the illness and with organ damage including vasculitis [10,46,58,67,89]. However, in the blood of the majority of young patients with arthropathy, the presence of anti-nuclear antibodies is found. ANA most frequently occurs in children with oligoarthritic type of JIA and less often in polyarticular type of RF (-) [67,81]. It is suggested that these antibodies may be markers of early-onset oligoarthritic JIA with accompanying inflammation of the uveitis [3,22,34,46,54,81]. Furthermore, it is claimed that the presence of ANA is

associated with a more severe course of the disease and with radiographic changes in joints [46].

The clinical activity of the disease and intensification of joint damage are also associated with anti-CCP which occurs in JIA patients' blood. The mentioned anti-CCP antibodies most often characterize patients with polyarticular, seropositive type of JIA, and their presence does not indicate the relation between the disease duration and the applied treatment modifying the course of the disease [4,10,46,89].

However, the presence of antibodies directed against the extracellular matrix components including aggrecan, which is the major proteoglycan in cartilage and which gives this tissue appropriate hardness, flexibility and elastic strength, is found more often in children who become ill at a younger age and require more aggressive therapy [4,10,36,44,46].

THE FATE OF GLYCOSAMINOGLYCANS IN THE COURSE OF JIA

Juvenile idiopathic arthritis is a non-homogeneous autoimmune children's disease which, despite the applied therapy, has a progressive character with recurrences leading to damage of joint structures. Progressive wearing of the joint cartilage in the course of JIA, which results from the imbalance between the biological strength of the cartilage, its function and exerted pressure forces, is linked to metabolic disorders of extracellular matrix (ECM) components [29,90,92]. Among the latter compounds, the proteoglycan (PG) aggrecan plays a particular role in maintaining the mechanical-immunological properties of the cartilage [6,29,36,75]. It is claimed that aggrecan degradation is a phenomenon occurring in early stages of arthritis, which initially concerns the joint surfaces and later on covers deeper layers of the mentioned structures [90,92].

Similarly to other proteoglycans, the aggrecan molecule is co-created by the core protein of a domain structure to which the heteropolysaccharide chains of glycosaminoglycans (GAGs) are attached, i.e. chondroitin-4-sulfate (of chondroitin sulfate A), chondroitin-6-sulfate (of chondroitin sulfate C) and keratan sulfates. Moreover, the core protein of aggrecan binds hyaluronic acid and forms a supramolecular complex [6,29,32,75]. Therefore, every change of ECM components' metabolism, linked to the increase of the rate of degradation or with the decrease of their biosynthesis, may have pathological consequences [6,75]. For instance, the intensified degradation of ECM macromolecules, which is characteristic for rheumatoid arthritis, causes gradual, often irreversible damage of the cartilage with a subsequent loss of joint mobility [32,88]. Metabolic changes of these structures, which are demonstrated by both the radiological picture and the profile of glycosaminoglycans in blood, are also found in the course of juvenile idiopathic arthritis [77,92,90,93]. In the case of untreated children with JIA, we observed a decreased concentration of GAGs in blood resulting from a substantial

reduction of sulfated glycans, particularly chondroitin sulfates [90,93]. Most likely, the observed changes reflect the enhanced tissue PG degradation occurring in early, pre-clinical stages of the disease. It is suggested that at the moment when clinical symptoms appear, the total amount of tissue GAGs is significantly reduced, while the processes of ECM components' synthesis do not compensate for the magnitude of degradation of these compounds. Therefore, in the blood of children with newly diagnosed JIA, the total amount of GAGs is significantly lower than in healthy children's blood [90]. Moreover, we found that the reduced concentration of the mentioned heteropolysaccharides in blood is accompanied by their decreased excretion with urine [93]. Furthermore, a decrease of the GAGs level in synovial fluid of JIA children was found [77].

Factors associated with catabolism of PGs and GAGs

The thesis of the intensified degradation of PGs/GAGs is confirmed by significantly higher concentrations of ADAMTS-4 (a disintegrin and metalloproteinase with thrombospondin motifs 4) or MMP-3 (metalloproteinase 3), found in blood, synovial fluid, or patient's saliva, and not balanced by the concentration of their tissue inhibitors, i.e. TIMP-1 (tissue inhibitor of metalloproteinase 1) and TIMP-2 [1,3,4,13,26,50,60,61,85,86,90,92]. Although the enzymes from the ADAMTS group are considered as major regulating factors of the aggrecan degradation processes, it is suggested that the concentration of MMP-3, which is significantly associated with both the plasma concentration of GAGs and the inflammatory marker CRP in children with JIA, may be an indicator of the disease activity and may allow the clinical progression of the disease to be anticipated [26,50,60,61]. The clinical consequences of high proteinase concentrations in blood of untreated children with JIA result not only in remodeling of the PGs/GAGs structure of joint cartilage but, by various mechanisms, may also lead to systemic disorders of the ECM in connective tissue. On the one hand, alongside depolymerisation of ECM protein components, MMP-3 is capable of activating other proteolytic enzymes, including pro-MMP-1, -3, -7, -8, -9 and -13, as well as of splintering cell adhesion molecules, chemokines and cytokines [25,39,47,60]. As a result of the mentioned actions, there may occur disturbances in cell proliferation and differentiation which are supported by the disturbed metabolism of GAGs, which, in turn, is stimulated by proteinases. It is widely known that glycans in the physiological state, due to high density of the negative electric charge, interact with many types of molecules including enzymes, growth factors and their receptors, transcription factors and structural proteins of the extracellular matrix [25,32,77,88,90]. Furthermore, despite typical characteristics for these compounds influencing cohesion, elasticity and the degree of hydration of the ECM, GAGs (particularly chondroitin sulfates) demonstrate antiinflammatory and antioxidative properties [14,15,20,23,25,43,49,83,87]. The first of the men-



tioned are associated with inhibiting the translocation of the nuclear transcription factor kappa B (NF- κ B) into the cell nucleus, with a progressive restriction of expression of genes encoding, among others, proinflammatory cytokines, chemokines, growth factors as well as acute phase proteins [83]. On the other hand, GAGs participate in the process of inhibiting caspase activation, restrict the expression and activity of proinflammatory enzymes, including cyclooxygenase-2 (COX-2), phospholipase A2 (PLA2), and nitric oxide synthase-2 (NOS-2), and reduce the toxic influence of reactive oxygen species (ROS) [20,43,49,87]. The antioxidative properties of heteropolysaccharide components of the ECM are associated with the ability of these compounds to chelate transition metals such as copper or iron, which are responsible for initiating the Fenton reaction, i.e. the transformation which generates ROS. Another antioxidant mechanism may be a direct scavenger effect of GAGs on the hydroxyl radical and superoxide radical [14,15,23]. Consequently, it can be concluded that the proteolytic degradation of ECM components in children with untreated JIA also weakens antioxidative mechanisms [90]. The latter protect the organisms against free-radical degradation, which is a link in the chain of pathogenic changes leading to JIA development [45,90]. Therefore, the prooxidative-antioxidative imbalances become yet another pathogenetic factor, alongside the excessive enzymatic proteolysis, which leads to PG/GAG metabolism disturbances in JIA children [45,90]. It is widely known that reactive oxygen species participate in the extracellular degradation of ECM components [55,59,91]. On the other hand, it is common knowledge that oxidative stress occurs in patients with JIA, which is demonstrated by increased free-radical activity and a weakened antioxidative system [13,45,90].

Factors affecting the biosynthesis of PGs and GAGs

Alongside excessive proteolysis, the dysfunction of joint structures in children with JIA may be supported by disturbed processes of biosynthesis of ECM components. It is known that the factors which have a significant influence on the biosynthesis of matrix components are insulin-like growth factor 1 (IGF-1), TGF- β and platelet-derived growth factor BB (PDGF-BB). The mentioned factors are multipotential cytokines which, apart from regulating the biosynthesis of matrix components, also regulate cell proliferation, differentiation, migration and cell apoptosis [12,21,25,56,70,84]. IGF-1 and PDGF-BB are potent inhibitors of IL-1 β -mediated activation of NF- κ B and apoptosis in chondrocytes [52]. However, in the course of JIA, different trends of concentration changes of the mentioned factors are observed. Therefore, while in patients with arthropathy a significant increase of TGF- β 1 and PDGF-BB concentration is observed, the concentration of IGF-1 slightly decreases or is comparable to that observed in healthy children [11,12,71,92]. Although the described compounds significantly influence the homeostasis of connective tissue components, it seems that TGF- β and PDGF-BB are factors that have a special role in this regula-

tion. On the one hand, both factors induce the proliferation of fibroblast-like synoviocytes (FLS), i.e. cells which secrete many connective tissue components including fibronectin, laminin, collagens and proteoglycans. On the other hand, activated FLS are also a source of proteinases degrading joint proteoglycan components [8,12,53,57]. Consequently, it may be concluded that the FLS, stimulated by PDGF and TGF- β , play an important role in the processes of both synthesis and degradation of PGs/GAGs [8,12]. Nevertheless, the glycosaminoglycan blood profile in children with JIA appears to indicate that in the course of the disease, the processes of ECM component synthesis are weakened when related to the magnitude of their catabolism. The thesis seems to be supported by the stimulating effect of PDGF and TGF- β on the processes of synthesis and release of pro-inflammatory cytokines including IL-6, IL-8, and MIP1 α by FLS [8,53,57]. Interestingly, in JIA patients with the clinically balanced disorder, PDGF and TGF- β occur in significantly lower concentrations when compared to those in healthy children's blood [92]. Therefore, it may be supposed that the pro-inflammatory cytokines, which lead to development of arthropathy in children, simultaneously induce the hypersecretion of PDGF and TGF- β , which, in turn, may intensify the cascade of changes leading to joint damage.

The influence of immunological processes on plasma total GAGs

The changes of ECM proteoglycans, which are reflected in GAG concentrations in the blood, in the course of JIA are complex. We have found that the treatment which modifies the inflammatory condition and leads to clinical improvement in children with JIA simultaneously does not lead to normalization of blood GAG concentrations [90]. Despite the increased concentration of these compounds in treated patients, which may indicate the ongoing regenerating processes in connective tissue, the level of GAGs is still significantly lower than in healthy children. Most likely, the observed changes of PG/GAG metabolism in children with JIA are also related to the auto-immune background of the disease. In the systemic circulation and in the synovial fluid of rheumatoid arthritis patients, the presence of GAG-specific antibodies was observed [28]. Their synthesis is likely to be up-regulated due to the extensive release of cartilage molecules. It is concluded that during the active phase of the disease, the levels of anti-GAG antibodies are reduced because of their binding to GAGs, released from the degrading cartilage [28]. As a result, the pool of plasma GAGs may also diminish. Moreover, it is suggested that the aggrecan core protein may be the first original target of auto-reactivity [36]. The auto-reactive lymphocytes, which migrate from the blood, accumulate in the area of joint structures, secrete significant amounts of pro-inflammatory cytokines, including IL-1, TNF- α and chemokines, and lead to pathological effects in the area of the cartilage or synovitis [36,57]. On the other hand, the adhesion properties of the glycosaminoglycan chains of aggrecan seem to favor the mentioned accumulation.

CONCLUSIONS

The alterations of ECM components' metabolism, associated with JIA disease, are reflected by quantitative changes in blood GAGs. The mechanisms leading to the mentioned disorders are complex and interconnected. The applied therapy with methotrexate, glucocorticosteroids, non-steroid anti-inflammatory drugs relieve the symptoms of JIA by alleviating both the pain and

the intensification of inflammatory processes, although it does not lead to total regeneration of the connective tissue elements damaged by proteolytic-oxidative factors and immunological processes. Taking into account the destructive potential of MMP, ADAMTS and ROS and their high expression in the course of JIA, the decrease in overproduction of these compounds in sick children with arthropathy should be clinically beneficial, which results from normalization of ECM components' metabolism.

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The authors have no potential conflicts of interest to declare.

