ADAMTS-4 as a possible distinguishing indicator between osteoarthritis and haemophilic arthropathy

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Abstract

Introduction: Osteoarthritis (OA) and haemophilic arthropathy (HA) are clinically similar, but pathologically distinct conditions which result in joint pain and loss of function. Distinguishing their disease mechanisms is therefore a key step in the development of curative therapy, as opposed to current symptomatic treatments. A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) 4 is a metzincin-family member proteoglycan with known local involvement in OA pathogenesis.

Aim: To investigate the potential differences and discriminatory potential of ADAMTS-4 between OA and HA patients.

Methods: We determined ADAMTS-4 plasma concentrations by ELISA in patients with HA and OA. This pilot cross-sectional study included N = 40 male participants equally divided across four subgroups: haemophilia patients with severe or mild HA and control subjects with severe or mild/no OA.

Results: Our study showed a striking elevation in plasma ADAMTS-4 expression levels in HA patients as compared to OA, as well as an increase in patients with severe as compared to mild HA. By performing the binomial logistical analysis and fitting the receiver–operator curve (ROC) (cut-off probability .5), ADAMTS-4 had a sensitivity of 95% and specificity of 50% in discriminating between HA and OA among our study participants.

Conclusion: Uncovering the marked differences in plasma levels of ADAMTS-4 in patients with HA versus OA potentially sheds new light on the mechanisms of HA pathogenesis and could foster more research into the roles ADAMTS-4 and other matrix metalloproteinases (MMPs) play in HA versus OA.

KEYWORDS
ADAMTS-4, a disintegrin and metalloproteinase with thrombospondin motifs 4, haemophilia, haemophilic arthropathy, metzincins, osteoarthritis
1 | INTRODUCTION

Osteoarthritis (OA) is a debilitating degenerative joint disease characterized by articular cartilage degradation, subchondral bone remodelling, osteophyte formation and localized inflammation. It is an increasing and leading cause of disability in the elderly that is usually accompanied by other risk factors such as obesity (bone-mass index), genetic variations, joint injury and abnormal joint biomechanics. These changes cause chronic joint pain, stiffness and loss of movement function. The aetiology of OA is still insufficiently known, although it is assumed that biochemical, mechanical and enzymatic factors play an important role in triggering the disease. A common pathway of all these factors is the imbalance between anabolic (anti-inflammatory and chondrogenesis) and catabolic events (inflammation and cartilage matrix degradation). OA shares some biological features with haemophilic arthropathy (HA), a progressive joint disease most caused by haemophilia. Although clinically similar, there are significant differences in their disease mechanism. It is important to discover and confirm the key molecules associated to the development of each condition. Previous studies describe HA as a degenerative arthropathy resembling OA, but recent evidence distinguishes HA by the complex inflammatory and immunologic mechanisms involved in its pathophysiology. Haemophilia is a genetic X-linked congenital bleeding disorder caused by the deficiency or absence of clotting factor VIII or IX (haemophilia A and B, respectively), and its most frequent manifestation in both children and adults is spontaneous joint bleeding. Another one of its major manifestations is HA, a serious joint disease caused by the aforementioned intra-articular bleeding. Target joints usually include large synovial joints that can haemorrhage multiple times over a single year, thus commonly progressing to severe, disabling HA. Recurrent bleeding changes the synovium by increasing vascular perfusion and inflammation, leading to chronic synovitis and destructive arthropathy. What is more, the blood-derived iron deposition induces chemical damage of the synovial membrane, which becomes hypertrophic and villous. The accumulation of haemosiderin triggers inflammation and inhibits synovial cell apoptosis by modulation of the expression myelocytomatosis viral oncogene (c-MYC) and mouse double mutant (MDM2) homologue. In the paper by Acharya et al., the authors highlight the role of mononuclear cells from patients with haemophilia in induction of VEGF-dependent synovial cell proliferation related to oxygen demand in inflamed and hypertrophic synovium. Furthermore, iron (released from haemoglobin) by itself induced expression of pro-inflammatory cytokines in synoviocytes like interleukin (IL)-1β, IL-6, IL-8 and interferon-γ, which enhance the catabolic activity and cartilage destruction. It seems that these mechanisms lead to an increased number of synovial cells, which can be considered resident tissue macrophages, as well as to an increase in their pro-inflammatory activity, ultimately leading to cartilage destruction. TNFα is one of the most studied inflammatory cytokines in HA because of its crucial role in its pathophysiology. It is important in regulation of joint bleeding and intra-articular levels of FVIIIa, inhibition of collagen type II and proteoglycan synthesis. It also causes induction of metalloproteinases, including ADAMTS-4, one of the most studied inflammasome activators and anti-inflammatory cytokines like interleukin (IL)-1β, IL-6, IL-8 and interferon-γ, which enhance the catabolic activity and cartilage destruction. Considering all of the above, we conducted a small pilot cross-sectional observational study in order to determine possible differences between ADAMTS-4 concentrations in patients with HA and OA, obtaining plasma from patients with both diseases in severe and mild stage. To the best of our knowledge, there are no published studies showing differences in ADAMTS-4 blood/plasma concentration between OA and HA patients. In this paper, we want to show that ADAMTS-4 plasma levels could be a distinguishing indicator between these two similar, but undoubtedly different conditions and, as well as to formulate the hypothesis regarding the potential role ADAMTS-4 plays in the pathogenesis of HA.
with haemophilia. Ultrasound evaluation was performed by a rheumatologist with more than 10 years of experience in ultrasound of the locomotor system. The control group consisted of blood samples provided by 10 ($N = 10$) healthy volunteers aged 30–53 years free of any active infections, malignant or other life-endangering disease. Further information regarding participants’ characteristics is shown in Supplementary Table S1.

### 2.2 Plasma sample collection

Blood samples (~5 ml per participant) were drawn by venipuncture and stored in vacuette blood collection tubes containing 3.8% sodium citrate (blood to anticoagulant ratio 1:9). Plasma was isolated by centrifugation at 1500 g for 15 min and stored at −80°C until further analysis.

### 2.3 Enzyme-linked immunosorbent assay (ELISA)

ADAMTS-4 in plasma samples was detected using an indirect ELISA kit (Human ADAMTS4 DuoSet ELISA DY4307-05 R&D, Minneapolis, MN), according to manufacturer’s instructions. Results were obtained with a plate reader (Molecular Devices—SpectraMax i3x) at 450 nm. All samples and standards were analysed in duplicates, and samples with an individual coefficient of variation (CV) greater than 25% were retested in duplicates. All procedures and evaluation of the results were conducted by two researchers blinded to clinical and pathological patient data.

### 2.4 Data analysis

Participants’ characteristics were summarized using descriptive statistics, parametric variables were reported as mean (±standard deviation), non-parametric variables as median (Q1–Q3) and categorical variables as number ($N$) or as ratio (percentage, %). Type I error (alpha) was set to .05. Formal assessment of ADAMTS-4 values between groups was performed using the Kruskal–Wallis one-way analysis of variance (ANOVA) test for non-parametric samples, after which Dwass–Steel–Critchlow–Fligner (DSCF) pairwise analysis was performed. Discriminative properties of determined ADAMTS-4 plasma values were assessed using logistical regression: (a) first, a multinomial logistical regression analysis was performed with four aforementioned groups as dependent variables, and ADAMTS-4 values set as a covariate, from which estimated marginal means (EMM) were reported; (b) second, three distinct binomial logistical regressions were performed by fitting receiver–operator curves (ROC) with a set cutoff point at .5. Binomial regressions were performed in order to test ADAMTS-4 as a potential discriminator (i) between patients with haemophilia and without haemophilia (irrespective of the HA/OA status); (ii) between patients with severe HA/OA versus mild/no HA/OA (irrespective of the disease pathophysiology, i.e. haemophilia status); (iii) between patients with severe HA versus severe OA. For the binomial analyses, a ROC curve was reported, alongside with specificity and sensitivity. Additional information regarding logistical regression was reported as Supplementary material. All analyses were performed in JAMOVI 1.6.23.
RESULTS

Participants’ main characteristics are presented in Supplementary Table S1. The group with severe HA had the highest concentration of ADAMTS-4 in their plasma, with a median of 34.3 (3.41–166) pg/ml. Medians of all other groups amounted to 0 pg/ml, however, a visible trend of declining levels of ADAMTS-4 is visible across the groups: the next being patients with mild HA, followed by patients without haemophilia: first by the group with severe OA and then by patients with no/mild OA (Figure 2(A)). A statistically significant difference among groups was observed ($\chi^2 13.1; p = .004$), DCSF pairwise comparison can be found in the Supplementary material 1. Multinomial regression analysis model was statistically significant ($\chi^2 11.4; p = .01$), derived EMMs are graphically depicted in Figure 2(B). Binomial regression analyses yielded the following results: ADAMTS-4 plasma values were shown to be discriminatory of (i) haemophilic versus non-haemophilic patients with 95% sensitivity and 50% specificity (Figure 2(C)); (ii) between patients with severe versus mild/no disease (regardless of disease pathophysiology) with 80% sensitivity, 25% specificity (Figure 2(D)); (iii) between severe HA versus severe OA patients with 90% sensitivity and 40% specificity (Figure 2(E)). Complete data regarding performed logistical regressions can be found in the Supplementary material.

DISCUSSION

In the present study, we determined for the first time the plasma levels of ADAMTS-4 in patients with mild and severe HA and OA in order to propose its distinguishing diagnostic and prognostic nature. Our results showed that ADAMTS-4 values determined by ELISA were the highest in the group of haemophiliacs with severe HA. Furthermore, ADAMTS-4 concentration levels appeared to be a sensitive (95%) but poorly specific (50%) indicator of haemophilia status across our sample. Furthermore, ADAMTS-4 levels also appeared to be able to distinguish between severe and mild/no disease with a sensitivity of 80%, but with low specificity (25%).

Previous research has been done to show an association between ADAMTS molecules and the severity of articular cartilage injury, but OA and HA were never compared in this regard. Both diseases result in progressive cartilage destruction, however, their distinct pathogenesis needs to be considered when investigating for markers of each disease. Li et al. observed the link between serum levels of ADAMTS-4, -5 and MMP-1 and -3 and the severity of OA. They concluded that ADAMTS-4 in mild OA patients was significantly higher than in other advanced OA groups and healthy controls. Significance of synovial fluid ADAMTS-4 and -9 levels in OA progression were evaluated, and no significant differences were found in ADAMTS-4.
The pathogenesis of articular cartilage damage in the two aforementioned conditions may have a different pattern that entails a different expression profile of molecules that are activated and lead to damage. As previously mentioned, the study by Li et al. found elevated serum levels of ADAMTS-4 in mild OA forms, which is in contrast to our findings, which show larger individual levels in severe OA compared to mild disease forms; the largest increase was observed in the group of patients with HA, which was not thus far explored by other authors. Although several members of the ADAMTS family are well known to play key roles in OA through degradation of the extracellular matrix (ECM) type II collagen and aggrecan, ADAMTS-4 in particular seems to be of more importance, or at least more specific to HA, which could be connected to its different aetiology and pathophysiology. Our research may have singled out HA (alongside with previously recognized OA) and implicated it as a new indication where circulating ADAMTS-4 could be tested as a more sensitive marker of disease activity and progression; however, larger and focused validation studies are required in order to test and confirm this. Existing research suggests that cytokines and matrix metalloproteinases (MMPs) may induce chondrocyte apoptosis in HA; joint bleeding and chemical damage of the synovial tissue induced by iron derived metabolites are associated with the production of reactive oxygen species (ROS). Direct harmful effects of intra-articular blood on cartilage are demonstrated by in vitro studies, which showed long-lasting inhibition of cartilage matrix proteoglycan synthesis. In HA, extravascular fibrin deposition could be critical in the interplay between inflammation and haemostasis, as plasmin increases activation of MMPs by proteoglycan release and leads to cartilage destruction. Therefore, it could be assumed that ADAMTS metalloproteinases are also activated by this process (Figure 3). Some authors proposed that ADAMTS-4 is induced by stimulation from catabolic agents, like tumour necrosis factor-α (TNF-α), interleukin 1-α (IL-1α), oncostatin M and transforming growth factor-β (TGF-β), which is not the case with ADAMTS-5; this suggests that they have different gene expression regulation. Induction of ADAMTS-4 by TNF-α and IL-1 has also been described in the setting of OA pathophysiology. Furthermore, research showed that ADAMTS-4 is one of the metalloproteinases induced by nitric oxide (NO) production, aided by monocytes/macrophages, which are in turn activated by TNF-α, a key player in HA pathogenesis. Both OA and HA present with underlying synovitis. In HA, it is caused by the presence of blood in the joint space, while in OA, it seems to involve the degradation products of extracellular matrices of cartilage and other joint tissues. ADAMTS-4 has already been proposed as an important enzyme in OA pathogenesis, as it partly mediates aggrecan degradation, which is a significant event in early-stage OA. This is also supported by the research of Roberts et al., who identified ADAMTS-4 as a possible biomarker of OA; however, it does not seem to be limited to OA, as they also found it to be a biomarker of joint inflammation in general. In HA, the resulting hemarthrosis causes inflammation and presumably triggers discrete inflammatory cytokines, resulting in changes of plasma ADAMTS-4 concentrations (which should be confirmed in future studies). This inflammatory process is characterized by synovial hypertrophy, neovascularization with increased circulating levels of VEGF-A, which correlates with disease activity in some conditions such as rheumatoid arthritis (RA). Synovial over-reaction leads to migration and activation of inflammatory cells, including monocytes/macrophages, which are a major source of ADAMTS-4: This could be reflected in the increase of its circulating levels in patients with HA (Figure 3).

Our study has several limitations which need to be addressed: the detection threshold of the commercially available ELISA kit we employed is relatively low; therefore it was not possible to discriminate between very low levels of ADAMTS-4 in plasma; which were all categorized as 0 pg/ml; this limitation might be a potential explanation for the contrasting differences we observed in comparison to Li et al. in OA patients. Furthermore, our pilot experiment was conducted as a single-centre cross-sectional study with a relatively small sample size of 10 male patients per group—further prospective studies in larger cohorts which could allow more elaborate experimental design and statistical analysis are needed to validate our present result. The presented specificity and sensitivity of the conducted analyses serve only an illustrative point—that is, they serve as vistas to potential new horizons for research with a larger number of participants.

In addition to its diagnostic and potentially prognostic potential, it has been argued that ADAMTS-4 might be a potential molecular therapeutic target for cartilage damages, and our results show...
that this might also be the case in HA.\textsuperscript{34} Identification of specific target molecules in distinct joint diseases is of great importance as researchers have established that the selective inhibition of ADAMTS molecules provides the possibility of modifying metalloprotease inhibitors to specifically target a class of cartilage-degrading proteinases.\textsuperscript{35} Therefore, we find ADAMTS-4 in the setting of HA an important topic to consider in future research, which aims to improve the quality of life and clinical outcomes of HA patients.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Lovorka Grgurevic and Natasa Kalebota. Investigation: Grgur Salai, Stela Hrkac, Rudjer Novak and Kristina Kovac Durmis. Methodology: Grgur Salai, Stela Hrkac, Rudjer Novak and Kristina Kovac Durmis. Formal analysis: Grgur Salai and Rudjer Novak. Visualization: Grgur Salai and Rudjer Novak. Supervision: Lovorka Grgurevic and Porin Peric. Validation: Lovorka Grgurevic and Porin Peric. Writing—original draft: Lovorka Grgurevic, Grgur Salai, Stela Hrkac, Rudjer Novak and Natasa Kalebota. Writing—review and editing: Natasa Kalebota, Grgur Salai, Porin Peric, Stela Hrkac, Rudjer Novak, Kristina Kovac Durmis and Lovorka Grgurevic. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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