

Original Article

Correlation of concentrations of activin A with occurrence and severity of knee osteoarthritis

L. Zou, J. Liu, H. Lu

Department of Orthopaedic Surgery, Jingzhou Central Hospital, Jingzhou 434020, Hubei Province, China

Abstract

Background: Activin A plays as an anticatabolic autocrine cytokine in articular cartilage. Thus, this study aims to evaluate whether activin A concentration is correlated with the occurrence and severity of knee osteoarthritis (OA). **Methods:** A total of 210 knee OA patients and 150 healthy controls were enrolled in this cross-sectional study, to evaluate the severity of OA by Kellgren-Lawrence (KL) grading method. **Results:** It was found that the concentration of activin A in knee OA group was higher than that in healthy subjects. Furthermore, results of of activin A concentration in serum and synovial fluid (SF) suggested that activin A concentration was the highest in Kellgren-Lawrence (KL) grade 4, and the lowest in KL grade 2. Concentrations of activin A in serum and SF showed significant correlation with disease severity measured by KL grading criteria. **Conclusions:** It was indicated that concentrations of activin A in serum and SF showed a positive correlation with the occurrence and severity of knee OA.

Keywords: Activin A, Severity, Occurrence, Knee Osteoarthritis

Introduction

Osteoarthritis (OA) is the most prevalent joint disease with typical characteristics, such as joint-space narrowing, and subchondral sclerosis, which induces swelling, reduces moving, stiffness and pain, and brings great cost burden to the society¹. Epidemiological evidences revealed a potential link between cartilage damage and inflammatory synovium², because inflammation exerted important effects on the occurrence and progression of OA even in the early stage³.

As a member of transforming growth factor- β (TGF- β) family, activin A performs various functions in different tissues. There are three forms of activin: activin A, activin B, and activin AB⁴. Activin A is released by various types of cells early and services as a part of the circulatory cytokine cascade in response to inflammatory compounds to participate

in the process of inflammation⁵. Recently, El-Gendi et al. (2010) reported that serum activin A concentrations were significantly increased in OA subjects in comparison with the controls⁶. In addition, activin A promoted the proliferation of fibroblast-like synoviocytes (FLS)⁷, resulting in the destroyed articular bone and cartilage in OA process. Therefore, we hypothesized that activin A might be a great regulator in OA development and progression.

This study was performed to explore the relationship between the concentration of activin A and the occurrence and severity of knee OA.

Materials and methods*Participants*

A total of 360 participants including 210 knee OA patients (case group) and 150 healthy participants (control group) were enrolled in this study. The case and control groups were in a matched age and gender distribution (Table 1). According to criteria specified in American College of Rheumatology, knee OA patients were diagnosed. Exclusion criteria for knee OA patients included malignant tumors, rheumatoid arthritis or inflammatory knee disease, corticosteroids medications, and systemic or autoimmune diseases. The participants in the control group were all with normal knee radiographs and would be excluded if they had arthritis history. This research

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Corresponding author: Lixue Zou, M.D. Department of Orthopaedic Surgery, Jingzhou Central Hospital, 60 Jingzhong Road, Jingzhou District, Jingzhou 434020, Hubei Province, China
E-mail: zoulixue66@hotmail.com

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Table 1. The characteristics between knee OA patients and healthy controls.

Characteristics	Knee OA patients (n=210)	Healthy controls (n=150)	P value
Age (years)	61.10±10.24	61.79±9.13	0.515
Gender (male/female)	77/133	61/89	0.442
Activin A in serum (pg/mL)	220.55±25.38	100.66 ±8.33	<0.001
Activin A in SF (pg/mL)	87.83±7.52	--	--

received approval from the Human Ethics Review Committee of Jingzhou Central Hospital. All participants signed the consent form.

Kellgren and Lawrence (KL) were applied for evaluation for severity of knee OA. Participants with KL grade ≥ 2 and 0 were considered as OA diagnosis and controls, respectively.

Laboratory methods

Blood was collected from the case and control groups and put in 1.5ml Eppendorf tube containing 7.5 μ l Heparin 1000 u/ml. Then blood samples were centrifuged at 14,000 rpm for 5 min at 4°C. Serum was separated and stored at -20°C for detecting the concentrations of activin A. SF was abstracted from the knees of OA patients before hyaluronic acid medication process. Commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D company, Farmington Hills, MI, USA) were used to measure concentrations of activin A in serum and SF.

Statistical analysis

Data were showed as a form of means \pm standard deviation (SD). The chi-square tests, unpaired t-test, or Mann-Whitney U test were used to compare case and control groups. Kruskal-Wallis test was applied for comparison of activin A concentrations among different KL grading. As for correlation between activin A concentrations and KL grading, spearman correlation analysis and multinomial logistic regression analysis were applied for analyzing the data. A P value <0.05 was considered to be statistically significant based on two-tailed tests.

Results

Concentrations of serum activin A between case and control groups

As shown in Table 1, the concentration of serum activin A (220.55±25.38 pg/mL, ranged from 177.50 to 252.18 pg/mL) in the case group was relatively higher than that in the control group (100.66±8.33, ranged from 76.73 to 118.30 pg/mL) ($P < 0.001$). Activin A concentration in SF was 87.83±7.52 pg/mL in knee OA patients, but there was no results obtained from the control group because they refused to take samples of SF.

Correlation of activin A concentration with KL grades

Results in Table 2 suggested that concentrations of activin A in serum and SF were the highest in knee OA patients with KL grade 4, and the lowest in KL grade 2. As evaluated by KL grading criteria, concentrations of activin A in serum and SF were found to be significantly related to the severity of disease.

Additionally, through spearman correlation analysis, a positive correlation between both concentrations of activin A and KL grades was found in serum ($r = 0.353$, $P < 0.001$) and SF ($r = 0.387$, $P < 0.001$). After multinomial logistic regression analysis, concentrations of activin A in serum ($P < 0.001$) and SF ($P < 0.001$) exhibited a significant correlation with KL grades (Table 2).

Discussion

Activin A was revealed to play an important role in occurrence and progression of OA. Previous study reported a significant higher serum activin A concentration in OA patients⁶. Another study also showed that activin A concentrations were promoted in OA cartilage compared to normal cartilage⁷. In this study, we also demonstrated the increase of activin A concentrations in patients with knee OA. In addition, our results revealed a close relationship between activin A concentrations and disease severity of OA. Nowadays, more and more studies have focused on the aspects of biomarkers which can be utilized to predict the disease in an early step and the prognosis of different disease. Therefore, our findings supported the idea that activin A concentrations could be a biomarker to predict risk for developing OA and evaluate severity of disease or progression of OA.

Numerous studies confirmed that activin A was involved in the pathogenesis of OA. For instance, activin A mRNA and protein were enhanced in dissection and culture of human or porcine articular cartilage, indicating a potentially anticatabolic role of activin A in articular cartilage⁸. Cartilage/joint injury in mice caused the increased expression of activin A gene⁹. Furthermore, as a key player in OA pathogenesis, fibroblast-like synoviocytes (FLS) could generate matrix degrading enzymes and pro-inflammatory cytokines, and erode cartilage and subchondral bone, which contributed to the development and progression of OA¹⁰. Recombinant activin A was found to promote FLS proliferation. On the

Table 2. The activin A concentrations in serum and SF of knee OA patients with different KL grades.

Activin A (pg/mL)	Grade 2 (n=67)	Grade 3 (n=92)	Grade 4 (n=51)	P value	r
Serum	196.00±23.46 [#]	218.24±37.79 [*]	241.97±21.35 ^{##}	<0.001	0.353
SF	79.42±12.32 [#]	87.34±10.28 [*]	103.24±18.23 ^{##}	<0.001	0.387

*P<0.01 vs KL grade 2; #P<0.01 vs KL grade 3.

other hand, follistatin, an endogenous activin antagonist, partially suppressed FLS proliferation induced by interleukin-1 β (IL-1 β)¹¹.

Inflammation is a clear mechanism of OA. It was reported that macrophages from rheumatoid arthritis (RA) joints promoted the acquisition of pro-inflammatory markers¹². However, anti-activin A-neutralizing antibody suppressed pro-inflammatory polarizing ability of macrophages, suggesting the important role of activin A in macrophage-derived cytokines production¹². IL-1, an inflammatory factor, could significantly increase the expression levels of activin A gene in chondrocytes^{13,14}. Furthermore, IL-1 β , TGF- β , and TNF- α activated FLS to secrete activin A¹¹. All those findings indicated that activin A was interacted with inflammatory molecules and might exert the effects on occurrence and progression of OA pathogenesis due to the increased and amplified inflammatory response in cartilage.

In conclusion, a close correlation between activin A concentrations in serum and SF and grading of knee OA was found in this study. However, the findings were limited and prospective investigation are still needed to be carried out to determine an exact role of activin A in OA.

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