Endothelin-1 concentrations are correlated with the severity of knee osteoarthritis

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ABSTRACT

Endothelin-1, a potent vasoconstrictor regulator, contributes to articular cartilage destruction. Therefore, we aim to assess the correlation of endothelin-1 concentrations with the development and severity of knee osteoarthritis (OA). This study included a population of 209 patients with knee OA. Kellgren-Lawrence (KL) grading was utilized to score the severity of OA. The case group had higher serum endothelin-1 concentrations than controls. Patients with knee OA with a relatively higher grade showed significantly elevated serum and synovial fluid (SF) endothelin-1 concentrations compared with those with lower KL grades. A significant correlation was found between serum and SF endothelin-1 concentrations and KL grades. Serum and SF endothelin-1 concentrations are correlated with the development and progression of knee OA.

Significance of this study

What is already known about this subject?

- Inflammation is a clear mechanism for osteoarthritis (OA) development.
- Many inflammatory factors are demonstrated to be correlated with OA development.
- Endothelin-1 contributes to cartilage degradation through inducing matrix metalloprotease (MMP) release.

What are the new findings?

- Patients with knee OA have significantly higher serum endothelin-1 concentrations compared with healthy controls.
- Serum and synovial fluid (SF) endothelin-1 concentrations are both associated with Kellgren-Lawrence grades.
- Serum and SF endothelin-1 concentrations are correlated with the presence and severity of OA.

How might these results change the focus of research or clinical practice?

- Serum and SF endothelin-1 concentrations could be utilized to predict the risk and progression of knee OA.

INTRODUCTION

Osteoarthritis (OA) is a common joint disease characterized by articular cartilage destruction and synovitis.[1] OA brought great healthcare burden to the society due to adverse effects on ambulation and mobility. OA is considered to be an inflammatory disease and inflammation is a clear mechanism for OA development.[2] Recent evidence showed that chondrocytes can produce a variety of inflammatory cytokines. Inflammation is a potential pathology for enhanced destruction of joint tissue, cartilage damage, and inflammatory synovium.[3]

The endothelins family, with three members including endothelin-1, endothelin-2, and endothelin-3, is originally identified in the vascular endothelial system.[4] Endothelin-1 is the main type among the three isoforms. In addition to vasoconstrictive and mitogenic properties,[5] endothelin-1 also plays a potential role in cartilage damage, which is a clear mechanism of OA development.[6] Recent evidence showed the promoting effects of endothelin-1 on cartilage degradation through inducing matrix metalloprotease (MMP) release.[6] The authors therefore came to the hypothesis that endothelin-1 may be a great regulator in OA development and progression.

This study was performed to determine the correlation of serum and synovial fluid (SF) endothelin-1 concentrations with the risk and progression of knee OA.

MATERIALS AND METHODS

Study population

We enrolled a population of 209 patients with primary knee OA for further study. Patients were excluded if they had inflammatory knee disease, systemic or autoimmune diseases, or a corticosteroids drug history. Patients were also excluded if they were confirmed with calcium pyrophosphate deposition disease (CPPD) crystals in SF. Control participants of 117 subjects were recruited and had no joint or systemic diseases. Informed written consent was signed by all subjects and the institutional review board of the institution approved this investigation.

Disease severity was scored using Kellgren-Lawrence (KL) grades. OA diagnosis was made if KL grade ≥2. KL grades of 0 for both knees were considered to be healthy controls.

Laboratory methods

SF was obtained from patients with OA during hyaluronic acid treatment. An ELISA kit (R&D

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Table 1 Characteristics between patients with knee OA and healthy controls

Characteristics	Patients with knee OA (n=209)	Healthy controls (n=117)	p Value
Age (years)	61.09±10.75	61.75±7.48	0.516
Gender (male/female)	88/121	46/71	0.623
Endothelin-1 in serum (pg/mL)	1.77 (1.43–2.02)	1.46 (1.16–1.81)	<0.001
Endothelin-1 in SF (pg/mL)	0.70 (0.60–0.84)		

OA, osteoarthritis; SF, synovial fluid.

Systems, Minneapolis, Minnesota, USA) was used to measure serum and SF endothelin-1 concentrations.

Statistical analysis

The results were in forms of means±SD or median (IQR). The characteristic differences between the cases and controls were determined by the Student t test, χ^2 tests or the Mann-Whitney U test. We used the Kruskal-Wallis analysis to determine endothelin-1 differences between different OA groups. Spearman correlation analysis and multinomial logistic regression analysis were performed to calculate the correlation of endothelin-1 with KL grades. p Value <0.05 was thought to be significant.

RESULTS

Clinical parameters between the two groups

There were no age and gender differences between patients with knee OA and healthy controls (table 1).

Serum endothelin-1 concentrations in the case and control groups

There were higher serum endothelin-1 concentrations in the knee OA group than in healthy controls (p<0.001) (table 1).

Endothelin-1 concentrations correlated with KL grades

Patients with knee OA with relatively higher grade showed significantly elevated serum and SF endothelin-1 concentrations compared with those with lower KL grades (table 2).

Correlation of KL grades with other variables

Serum and SF endothelin-1 concentrations were demonstrated to be related to KL grades using Spearman correlation analysis (r=0.358, p<0.001 and r=0.367, p<0.001). A significant relation between serum and SF endothelin-1 concentrations and KL grades was also shown by multinomial logistic regression analysis (p<0.001 and <0.001).

DISCUSSION

Recent evidence has indicated the important role of endothelin-1 in OA development. Appleton *et al* examined the different gene expression changes in articular chondrocytes from degenerated cartilage and found endothelin as one candidate gene associated with articular cartilage destruction.[7] A degenerated cartilage end plate showed higher endothelin-1 production than controls.[8] Endothelin-1 concentrations in serum and SF samples were higher in patients with rheumatoid arthritis (RA) than in healthy volunteers. Furthermore, SF endothelin-1 concentrations showed no marked differences between patients with OA and patients with RA.[9] It indicates that OA patients also had high serum endothelin-1 concentrations than the controls. This is supported by our findings showing higher endothelin-1 concentrations in patients with OA. In addition, endothelin-1 was found to serve as a promoting regulator in chondrocytes or joint destruction and OA development. Endothelin receptor type A antagonist treatments showed preventive effects on the joint cartilage destruction in a rat model of OA.[10] Articular chondrocyte ageing is a potential pathogenesis of OA development. Khatib *et al*[11] reported that old chondrocytes showed more endothelin-1 expression and possessed more endothelin-1 receptors with a higher affinity compared with relatively young ones. All these evidences support the promoting role of endothelin-1 in OA development and progression.

Inflammation contributes to OA development. Endothelin-1 is closely correlated with inflammation and takes part in OA pathogenesis via promoting inflammation. Interleukin-1β (IL-1β) and tumor necrosis factor α (TNFα) could stimulate the production of endothelin-1 with a concentration-dependent manner in articular chondrocytes.[11 12] TNFα also exhibited a dose-dependent stimulation on the expression of endothelin-1 in a cartilaginous end plate.[8] Incubation with IL-1β increased endothelin-1 binding sites in cultured rat articular chondrocytes.[13] In addition, endothelin-1 could induce the expression of nuclear factor κB, TNF-α, IL-1, and IL-6.[4]

MMP is involved in the process of extracellular matrix remodeling, cartilage degradation, and joint pathology which occurs under OA condition.[14] Endothelin-1 induced MMP-1 and MMP-13 releases in the OA chondrocyte.[6 15] Furthermore, endothelin-1 increased MMP-1 and MMP-13 production in the cultured cartilaginous end plate.[8] Therefore, endothelin-1 might serve as a regulator in the progression of OA pathology by initiating MMP release.

Table 2 Endothelin-1 concentrations in serum and SF of patients with knee OA with different KL grades

Endothelin-1 (pg/mL)	Grade 2 (n=58)	Grade 3 (n=93)	Grade 4 (n=58)	p Value
Serum	1.53 (1.28–1.85)*	1.75 (1.40–1.96)†	1.95 (1.67–2.14)*†	<0.001
SF	0.64 (0.55–0.73)*	0.71 (0.59–0.84)†	0.84 (0.65–0.92)*†	<0.001

*p<0.05 vs KL grade 3.
†p<0.05 vs KL grade 2.
KL, Kellgren-Lawrence; OA, osteoarthritis; SF, synovial fluid.

In short, serum and SF endothelin-1 concentrations were correlated with the risk and progression of knee OA.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The research ethics committee of Tianjin Hospital.

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