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Correlation of Adrenomedullin Concentrations with Knee Osteoarthritis Grade

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Background: Adrenomedullin, a recently identified myokine, has an anti-inflammatory effect. Therefore, we aimed to assess the correlation of adrenomedullin concentrations with the presence and grade of severity of knee osteoarthritis (OA).





Material/Methods: We recruited 187 knee OA patients and 109 healthy subjects. The severity of OA was evaluated using the Kellgren-Lawrence grading system.

Results: Compared with the control group, the knee OA group revealed markedly higher adrenomedullin concentrations. Serum and synovial fluid (SF) adrenomedullin concentrations increased with increased KL grades.

Conclusions: Serum and SF adrenomedullin concentrations show a correlation with the severity of knee OA.

MeSH Keywords: **Adrenomedullin • Biological Markers • Osteoarthritis, Knee • Severity of Illness Index • Synovial Fluid**

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Background

Osteoarthritis (OA), a chronic degenerative joint disease, is characterized by articular cartilage degradation, subchondral bone damage, and synovitis [1]. OA creates a great healthcare burden on society due to decreased 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 plays a key role in the destruction of joint tissue and it causes cartilage damage and inflamed synovium [3].

Adrenomedullin, a 52-amino-acid peptide, was originally identified in human pheochromocytoma [4]. Adrenomedullin is expressed not only in the cardiovascular system, but also in bone and joint structures. Besides its potent vasodilatory and hypotensive effects, adrenomedullin also has an anti-inflammatory effect [5]. Adrenomedullin can inhibit the production of tumor necrosis factor- α (TNF- α) from activated macrophages [6] and was found to abrogate inflammation and alleviate systemic bone loss in murine collagen-induced arthritis [7]. Adrenomedullin may be involved in the pathogenesis of OA through the anti-inflammatory effect.

We performed this cross-sectional study to determine whether adrenomedullin concentrations are related with the occurrence and severity of knee osteoarthritis.

Material and Methods

Patients

This cross-sectional study was performed in 187 knee OA patients (case group) and 109 healthy subjects (control group) matched for age and sex. Knee OA was diagnosed in accordance with the criteria of the American College of Rheumatology. The exclusion criteria were: inflammatory knee disease or rheumatoid arthritis, malignant tumors, systemic or autoimmune diseases, and corticosteroid medications. Control subjects were recruited from healthy subjects coming in for medical check-ups at our hospital, had normal knee radiograph results, and no arthritis history. Subjects with systemic disease and inflammatory disease were excluded from the control group. The study protocol was approved by the Human Ethics Review Committee of our hospital and a signed informed consent was obtained from each subject.

The Kellgren and Lawrence classification was used to evaluate the disease severity of knee OA. If either knee was assessed as KL grade ≥ 2 , an OA diagnosis was made. Controls were defined as both knees assessed as KL grades of 0. The higher grade of the 2 knees was used for analysis.

Laboratory methods

Serum was drawn from all subjects during the morning. SF was drawn from the knee before hyaluronic acid medication. Serum and SF adrenomedullin concentrations were then determined by using a commercial enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, MN, USA) [coefficient of variations (CVs) for intra-assay: 5–8%; CVs for inter assay: 10–14%; detection limit range: 0.2–150 pg/mL].

Statistical analysis

The results are expressed as means \pm SD or median (interquartile range). The differences in variables between the case and control groups were compared using chi-square tests, unpaired t-test, or Mann-Whitney U test, as appropriate. The Kruskal-Wallis test was used to compare adrenomedullin concentrations between knee OA patients with different grades of disease severity. The Mann-Whitney U test was then used to compare the adrenomedullin concentration differences between the 2 groups with different KL grades. Spearman correlation analysis and multinomial logistic regression analysis were used to evaluate the correlation of adrenomedullin concentrations with KL grades. *P*-value <0.05 was considered to be statistically significant.

Results

Clinical parameters between the 2 groups

No age or sex differences were observed between the case and control groups (Table 1).

Serum adrenomedullin concentrations in the case and control group

There were increased serum adrenomedullin concentrations in the case group compared to the control group ($P<0.001$) (Table 1).

Adrenomedullin concentrations correlated with KL grades

As KL grades increased, serum and SF adrenomedullin concentrations also increased (Table 2).

Correlation of KL grades with other variables

Spearman correlation analysis showed a positive correlation of serum and SF adrenomedullin concentrations with KL grades ($r=0.322$, $P<0.001$ and $r=0.373$, $P<0.001$). Multinomial logistic regression analysis also showed a significant association of

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

Characteristics	Knee OA patients (n=187)	Healthy controls (n=109)	P value
Age (years)	61.45±10.74	61.75±7.72	0.783
Gender (male/female)	76/111	43/66	0.840
Adrenomedullin in serum (pg/mL)	62.60 (50.98–72.00)	40.09 (29.81–48.58)	<0.001
Adrenomedullin in SF (pg/mL)	20.22 (17.04–24.26)		

Table 2. The adrenomedullin levels of serum and SF in knee OA patients with different KL grades.

Adrenomedullin (pg/mL)	Grade 2 (n=52)	Grade 3 (n=82)	Grade 4 (n=53)	P value
Serum	57.06 (44.81–66.04)**	62.05 (50.84–68.60)*	70.25 (58.23–75.53)***	<0.001
SF	18.67 (15.74–20.72)**	20.45 (16.89–23.55)	23.86 (18.50–26.67)***	<0.001

* $P < 0.05$ vs. KL grade 2; ** $P < 0.05$ vs. KL grade 3.

serum and SF adrenomedullin concentrations with KL grades ($P < 0.001$ and $P < 0.001$).

Discussion

A recent study showed that patients with rheumatoid arthritis (RA) and OA had relatively higher plasma adrenomedullin concentrations compared with healthy controls [8]. Our investigation also showed similar results regarding the differences in adrenomedullin levels between OA patients and controls. Treatment with adrenomedullin resulted in considerably fewer apoptotic chondrocytes and diminished cartilage degradation in a mouse model of arthritis [7]. After the injection of adrenomedullin into the knee joint spaces, rabbits with antigen-induced arthritis showed decreased joint swelling [9]. These results suggest that adrenomedullin plays a protective role in the development of OA. Elevated circulating adrenomedullin concentrations were also found in other inflammatory diseases, such as periodontal disease [10] and ankylosing spondylitis [11]. This indicates that elevated circulating adrenomedullin concentrations result from inflammatory disease status.

Fibroblast-like synoviocytes (FLS) play an important role in OA pathogenesis. FLS contributed to the OA development and progression via producing pro-inflammatory cytokines and matrix degrading enzymes, and eroding the cartilage and subchondral bone [12]. Adrenomedullin was found to inhibit interleukin (IL)-1 β -induced proliferation of FLS and the production of matrix metalloproteinases, cyclooxygenase, and prostaglandin E2 [13]. Two general mechanisms contribute to synovial hyperplasia and OA development: increased FLS proliferation and decreased synoviocyte apoptosis [14]. Adrenomedullin induced

rapid intracellular cAMP production and reduced caspase-3 activity, DNA fragmentation, and chromatin condensation in FLS exposed to apoptotic conditions, indicating that adrenomedullin may prevent or reduce FLS apoptosis [15]. Therefore, adrenomedullin may protect against cartilage damage and OA development through an effect on FLS.

Inflammation is involved in the mechanism of OA. Injection with adrenomedullin in knee joint spaces of rabbits reduced edematous changes and infiltration of inflammatory cells in the synovial tissues. In addition, adrenomedullin significantly reduced the expression levels of TNF- α [9]. In a mouse model of arthritis, adrenomedullin treatment shifted the pattern of articular and systemic cytokine expression from Th1 to Th2. Furthermore, TNF- α , IL-6, and IL-17A levels were significantly decreased in the joints of mice after adrenomedullin treatment.

The limitations of the present study should be considered. First, this was a cross-sectional study performed in a relatively small sample. Therefore, our findings should be validated by further longitudinal studies with larger sample sizes. Second, we did not assess the differences in adrenomedullin concentrations in SF between knee OA patients and healthy controls due to ethical concerns.

Conclusions

Serum and SF concentrations of adrenomedullin are positively correlated with grade of knee OA.

Conflict of interests

All authors have no conflict of interests to declare.

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