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# Experimental Study on the Changes of Sphingosine 1-Phosphate and Matrix Metalloproteinases 3 in Serum of Patients with Osteoarthritis

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**Abstract:**

**Objective:** To explore the level changes and clinical significance of matrix metalloproteinase-3 (MMP-3) and sphingosine 1-phosphate (S1P) in the patients with osteoarthritis (OA).

**Methods:** Thirty-six patients with early-stage OA and thirty-two patients with late-stage OA were selected. Besides, seventy-two age-matched healthy subjects who had the physical examination were also included as the control group. And the differences between S1P and MMP-3 levels in the three groups were also observed to investigate the correlation between S1P and MMP-3.

**Results:** In the early-stage OA group, the S1P and MMP-3 levels in serum are 0.118 ± 0.04 and 207.9 ± 19.70 pg/mL; S1P and MMP-3 levels in the late-stage OA group are 0.171 ± 0.03 and 292.23 ± 27.4 pg/mL. These values are both obviously higher than those in control group (S1P: 0.065 ± 0.02 pg/mL, MMP-3: 59.62 ± 8.38 pg/mL, $P < 0.05$). Analysis of spearman correlation revealed the positive correlation between levels of S1P and MMP-3 ($r = 0.740$).

**Conclusion:** The levels of S1P and MMP-3 showed an increase in the serums of OA patients; and the increased levels of S1P will result in the increased levels of MMP-3 and thus lead to OA, which is more obvious in late-stage patients.

**Keywords**: Osteoarthritis; Early-stage; Late-stage; Serum; Sphingosine 1-phosphate; Matrix metalloproteinases 3; Correlation

## 1. Introduction

Osteoarthritis (AD) has the ability to contribute to arthralgia and joint disorders as a consequence of the degenerative joint condition of soft bone fractures, subchondral bone degeneration, periarticular tissue reactive hyperplasia and large lesions synovative inflammation. The occurrence of OA has progressed after years of study, but the pathogenesis of OA remains uncertain. As a very powerful mediator for lipid diseases, S1P was developed primarily in the sphingomyelin plasma membrane catalyzed by sphingosine kinase [2].

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S1P 's major organic roles comprise: cell transmittal of a cell signal receptor and serving as a messenger; the synthesis of the required cell-binding sites by selective secretions in the extracellular space and cell surface; and, ultimately, the cell secretion, proliferation and celled aggregation modulation to accomplish the regulating immune system[3-4]. The hydrolysis of the cellular matrix [5] plays an essential role for the metalloproteinases (MPMs), which are affected concurrently by many ions within and out of a cell. The mechanism is also affected by many ions. The studies found that in patients with osteoarthritis the production of MMPs has been irregular in all forms of joint cavity tissues, and MMPs growing induce bone resorption in the subchondrel bone. Matrix metalloproteinases 3 (MMP-3) are secreted and released by osteoclasts that are targeted at soft bone cells mediated degradation and resorption of soft bones [6-7]. In the related literature, MMP-3 has also been proposed as an essential component in

inflammatory and degenerative diseases of the joint [8-9]. It is also not known how the OA is influenced by S1P and MMP-3, if it is linked to each other, and whether the similarity between patients in early stage or late stage OA is pathological and pathogenic. This research has therefore analyzed the levels of speech and the relation between S1P and MMP-3 in OA in detail. The following is the article.

## 2. Object and Method

### 2.1. Topic of the analysis

Around January 2016 and July 2017, 68 OA patients were taken from the orthopedic clinic from the hospital for ambulatory and emergency events. There were 42 men and 26 women with an age of 61,47 ± 6,86. OA patients' clinic condition was compatible with the "Osteoarthritis Evaluation and Care Order," excluding rheumatoid arthritis cases or other joint bone system diseases. There were 36 early stage AO patients (O.A. diagnosis verified and the duration of illness was no longer than 2 years) and thirty-two late stage AO patients (O.A. diagnosis verified and the duration of arthritis extended two years). Moreover, 72 paired age stable participants from both institutions, including 35 men and 37 women, have been chosen as standard test groups with an average age of 62.39 Ñ 7.48 and both registered informed consents. In gender, age, and other general details between the early-stage OA group, the late-stage OA group, and the control group, there was no apparent distinction suggesting they were comparable.

### 2.2. Form of the experiment:

The subjects obtained 1.5 mL of median vein blood, centrifuged at 3000 r / min for 10 min. For the determination of expression of S1P and MMP-3 in serum, a surnatant serum was isolated and deposited at -80 ° C. The amount of S1P and MMP-3 was reached by ELISA and the kits from Millipore (Merck, Germany) were received. All activities were done as per the instructions.

### 2.3. Process for statistics

SPSS 18 statistical software was used to evaluate all the results. The data were provided as (talking about s). A different t-test method for analyzing all classes has been added. A linear regression P < 0 was tested for the association of both classes. 05 suggests a statistically important gap.

## 3. Results

### 3.1. The expressions of S1P and MMP-3 in serum

The expression levels of S1P and MMP-3 in control group were obviously lower than those of early and late stage OA patients ($P < 0.05$), as shown in Table 1.

*Table 1.* **Expression levels of S1P and MMP-3 in serum of early-stage OA patients (□ ± s)**

| Group | S1P (pg/mL) | MMP-3 (pg/mL) |
|---|---|---|
| Early-stage OA | 0.118 ± 0.04*△ | 207.79 ± 19.70*△ |
| Late-stage OA | 0.171 ± 0.03* | 292.23 ±2 7.4* |
| Control group | 0.065 ± 0.02 | 59.62 ± 8.38 |

*Compared with the control group, *$P < 0.05$; compared with late-stage OA group, △$P < 0.05$

### 3.2. The correlation between S1P and MMP-3 in serum

The correlation of S1P and MMP-3 levels in the serums of all subjects was analyzed (Figure 1). It shows that the correlation between the levels of S1P and MMP-3 is significantly positive (r = 0.740, P < 0.01).

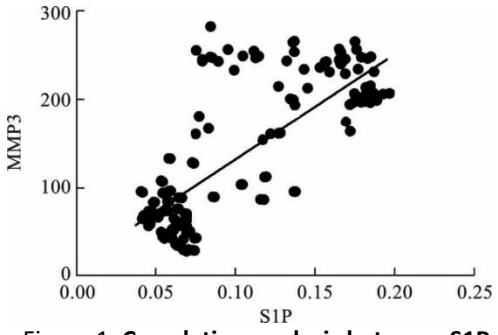


Figure 1. **Correlation analysis between S1P and MMP-3 in OA patients**

## 4. Discussion

OA is a progressive degenerative disorder marked by articular cartilage matrix degeneration, cartilage hyperostose and development of the osteophyte. OA has become a very serious bone condition in an ageing population and many OA patients feel tremendous pain in this regard. Up until now, osteoarthritis pathogenesis is also unknown. However, developments in OA therapy can be done only by recognizing the pathogenesis, which has become a hot subject for study among domestic and foreign scholars.

In several different types of cells, including platelets, red blood cells, (RBCs) and monocytes, S1P may be generated. Human serum has been documented to produce elevated S1P amounts,

from nano-molarity to micro-molarity. S1P has many roles such as controlling immune responses and angiogenesis [10–11]. Masuko et al [12] have noticed that S1P can participate by controlling expression of VEGF in chondrocytes in pathophysiology for OA. The role of S1P in bone metabolism has now been shown through substantial experimental validating. osteoclast secreted S1P facilitates osteoblast invasion, replication, and longevity [13]. [13]. The therapeutic reference value of MMP-3 is essential in articular cartilage lesions and persistent inflammatory bone metabolism. The serum in OA patients raised the MMP-3 concentration substantially to promote the absorption and restoring of damage through the modulation of cell proliferation factors in the bone and cartilage tissues [14]. Studies indicate that MMP-3 controls proteoglycan cartilage and cleaves the central proteins. The weakening of the cartilage matrix results, thus, in an atrophy of the chondrocyte function and loss of cell funtion due to reduction and loss of glycosaminoglycan debris, when the core proteins are decreased in OA. While S1P and MMP-3 play a key role in OA, the question whether they are related and if they jointly influence the pathogenesis of OA remains urgently essential.

The findings of this analysis found that in patients with early stage OA, S1P and MMP-3 in serum had been dramatically raise, indicating the pathogensis of early stage of OA was involved in S1P and MMP-3. Positively linked were the S1P and MMP-3, which showed that the S1P was better than standard monitors. The rise in S1P levels is hypothesized to greatly improve the stimulative impact of MMP-3 and to enable a rise in MMP-3. Several studies have also documented S1P 's possible function in the expresses of MMPs in cells [15]. Strong inhibitors in sphingosine kinase can, in this regard, prevent MMP expression and play a role in arthritis against inflammation [16]. In the Ustyol et al studies S1P was shown to be associated favorably with MMP1 and MMP-3[17], as the findings of this analysis are clear. Here the level of S1P and MMP-3 in early-stage OA patients was considerably less than the level of late-stage OA patients, which suggested that development of bone loss and disease intensity is strongly correlated with S1P and MMP- 3 markers, which illustrates the pathological function of the abnormally elevated signal behavior in patients with late- stage OA

This study further validates the idea that S1P can control the immune network functions such as MMPs at the start of early stage OA. A new approach for OA prevention and treatment could be a greater understanding of S1P 's function in extracellular matrix

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