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Matrix Metalloproteinase, Tissue Inhibitor of Metalloproteinase and Transforming Growth Factor-beta in Frozen Shoulder, and Their Changes as Response to Active Stretching and Gentle Thawing Exercise

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Summary:
The changes of MMP-1, MMP-2, TIMP-1, TIMP-2, and TGF-beta levels are related to the pathogenesis of frozen shoulder, and also to the improvement of the disease after physical exercise.

Abstract:
Background:
Frozen shoulder or idiopathic adhesive capsulitis of the shoulder is a disorder characterized by thickening and contracture of shoulder joint capsule that can be lasting for years. Several studies reported proteins correlated with frozen shoulder are matrix metalloproteinase (MMP), tissue inhibitor of metalloproteinase (TIMP) and also cytokines (e.g. TGF-beta). However, specific factors or mechanism involved in pathogenesis of frozen shoulder is still unknown. Analysis of circulated MMP and its inhibitor can describe extracellular matrix turnover, including fibrosis. Physical therapy in frozen shoulder has shown a good result but no experiment has explored the correlation between the improvement with the biochemical parameter of MMP, TIMP and TGF-beta. Here, we measured the serum level of those parameters before and after two types of physical exercise, i.e. active stretching and gentle thawing.

Methods:
Levels of MMP-1, MMP-2, TIMP-1, TIMP-2, and TGF-beta serum was measured from frozen shoulder patients and normal subjects. Functional assessment of shoulder joint in frozen shoulder patients was based on abbreviated Constant score. Frozen shoulder patients were then randomly divided into two physical therapy groups, i.e. active stretching and gentle thawing. Every week frozen shoulder patients were monitored for their compliance in performing their daily physical exercise. Abbreviated Constant score assessment and serum sample collection of frozen shoulder patients were done at baseline, and at week 6 and week 12 of exercise. Serum MMP-1, MMP-2, TIMP-1, TIMP-2, and TGF-beta were assayed using ELISA technique. MMP/TIMP ratio was calculated from the total sum of MMP-1 and MMP-2 levels divided by the total sum of TIMP-1 and TIMP-2 levels.

Results:
Mean serum level of MMP-1, MMP-2, TIMP-1, TIMP-2, MMP/TIMP ratio, and TGF-beta at baseline showed significant difference between frozen shoulder and control groups ($p=0.001$). MMP-1 and MMP-2 levels were significantly lower in frozen shoulder group than those in control group. TIMP-1, TIMP-2, and TGF-beta levels were significantly higher in frozen shoulder group than those in control group. In frozen shoulder group, MMP/TIMP ratio was significantly lower than in control group.
Physical exercise also affected the evolution of serum level of MMP-1, MMP-2, TIMP-1, TIMP-2, and TGF-beta. At week sixth and twelfth after exercise there was increase of MMP-1 and MMP-2 levels, whereas serum levels of TIMP-1, TIMP-2, and TGF-beta were decreased. MMP/TIMP ratio at week sixth and twelfth after exercise was also increased. Comparing the two groups of physical exercise, active stretching and gentle thawing, it was found that the increase of MMPs and decrease of TIMP and TGF-beta were more significant in active stretching group than those in gentle thawing group. Constant score was more significantly increased in active stretching group than in gentle thawing group.

Conclusions:
There is correlation between serum levels of MMP-1, MMP-2, TIMP-1, TIMP-2, and TGF-beta with frozen shoulder. It was found that the lower MMP-1 and MMP-2 levels, the higher risk of frozen shoulder, whereas the higher TIMP-1,

TIMP-2, and TGF-beta levels, the higher risk of frozen shoulder. Thus, the lower MMP/TIMP ratio the higher risk of frozen shoulder.
Active stretching can accelerate the improvement of frozen shoulder better than gentle thawing, as demonstrated by the improvement of Constant score and the biochemical parameters.