

Diabetes and shoulder disorders

Musculoskeletal disease is one of the most common complications in patients with diabetes, and yet it receives relatively little attention. The severity and the risks of musculoskeletal complications might not be well recognized as cardiovascular complications; however, the associated ailments certainly inflict both physical and psychological harm on people with diabetes. Among the various musculoskeletal diseases, shoulder pain is one of the most common complaints. In general, it is characterized by pain and limited range of motion of one or both shoulders. Shoulder pain not only causes decreased quality of life, but also leads to disability in daily activities, and might interfere directly or indirectly with control of metabolic processes.

Previous reports showed that there is a higher prevalence rate (27.5%) of shoulder disorders in patients with diabetes as compared with the rate of 5.0% found in general medical patients¹. Two of the most common shoulder disorders are frozen shoulder, also known as 'adhesive capsulitis' and rotator cuff disease. Frozen shoulder is characterized by progressive pain, stiffness, limited active and passive range of motion of the shoulder joints, especially external rotation, and night pain. Although the exact causes of frozen shoulder are still underexplored, it is generally believed that frozen shoulder develops as a result of perivascular inflammation and fibroblastic proliferation, followed by capsular fibrosis and contracture. It is worth noting that primary frozen shoulder is idiopathic and secondary frozen shoulder might be associated with previous shoulder injury, such as rotator cuff injury, trauma or prolonged immobilization. Clinically, frozen shoulder is diagnosed by history and physical examination. Current available managements include use of analgesia, such as non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol and/or intra-articular steroid injection, and can be combined with local anesthetic applications. Encouragement of activity is also crucial. Once the symptoms of pain and inflammation have reduced, gentle stretching and exercises that enhance the range of motion should be encouraged. In rare cases, surgical procedures can be considered, such as manipulation under anesthesia or capsular release under arthroscopic guidance.

The rotator cuff consists of the supraspinatus, infraspinatus, teres minor and subscapularis muscles. It originates from the scapula, and forms tendons that cover the humeral head. The rotator cuff provides important dynamic motor control and stability of the shoulder joint. Known risk factors of rotator cuff disease include old age, abnormal shoulder structure, certain sports and occupations that require excessive overhead activities. Rotator cuff disorders range from simple inflammation to

complete tendon tears, most frequently involving the supraspinatus tendon. The symptoms include shoulder pain, decreased muscle strength and particularly limited active range of motion. Clinically, taking a detailed history plus physical examination can help with the diagnosis. Imaging studies, such as ultrasound and magnetic resonance imaging, can confirm the diagnosis and provide further information of the severity and the extent of rotator cuff disease. Conventional radiograph is also helpful for making a more advanced differential diagnosis, and for ruling out bony abnormalities and tendon calcification. Management of rotator cuff disease includes NSAIDs, steroid injection, stretching and strengthening exercises for the shoulder. Surgical repair might be required in severe cases, such as complete tear of rotator cuff.

The association between rotator cuff disease and diabetes has yielded inconsistent results. To investigate the effect of diabetes on the occurrence of rotator cuff disorder, we analyzed nationwide data from the National Health Insurance Research Database in Taiwan². A total of 498,678 participants, including 28,391 diagnosed with diabetes and 25,621 with hyperlipidemia in the year 2000, were followed for an 11-year period. Multivariate Cox proportional hazards models were used to explore the effect of: (i) diabetes; (ii) hyperlipidemia; (iii) diabetes with/without insulin use; and (iv) hyperlipidemia with/without statin use on the development of rotator cuff diseases. We found that, during the follow-up period, 26,664 patients developed rotator cuff diseases with a crude hazard ratio (HR) of 2.11 for patients with diabetes as compared with those without diabetes (95% confidence interval [CI] 2.02–2.20, $P < 0.0001$). The crude HR for rotator cuff disease in patients with hyperlipidemia as compared with those without hyperlipidemia was 2.00 (95% CI 1.92–2.08, $P < 0.0001$). The results of multivariate Cox proportional hazards analysis showed that, in addition to older age and female sex, both diabetes and hyperlipidemia increased the risk of rotator cuff diseases (diabetes HR 1.47, 95% CI 1.41–1.54, $P < 0.0001$; hyperlipidemia HR 1.48, 95% CI 1.42–1.55, $P < 0.0001$). We also found that the elevated risk still existed in patients with diabetes with/without insulin use (diabetes with insulin use HR 1.43, 95% CI 1.35–1.51, $P < 0.0001$; diabetes without insulin use HR 1.64, 95% CI 1.53–1.75, $P < 0.0001$). Our findings confirmed that patients with diabetes, regardless of insulin use, had a higher risk of developing rotator cuff diseases. Our findings are in accord with previous imaging studies showing that degenerative changes of rotator cuff tendon were more commonly observed by sonography in patients with diabetes than in controls³.

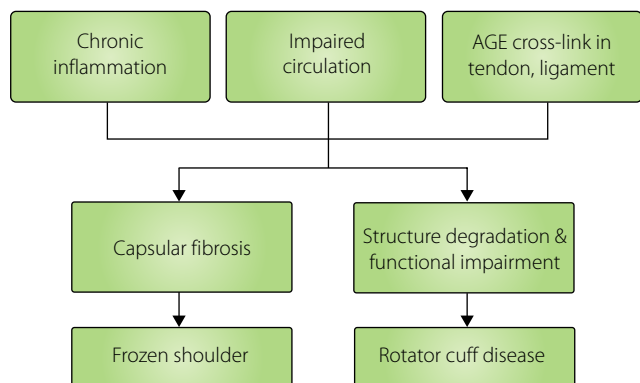


Figure 1 | Potential mechanisms of frozen shoulder and rotator cuff disease development related to diabetes. AGE, advanced glycosylation end-product.

The mechanism by which diabetes influences the development of frozen shoulder or rotator cuff disease has not been identified. The two diseases might share the same diabetes-related mechanisms: (i) impaired microcirculation; and (ii) non-enzymatic glycosylation processes (Figure 1). In fact, hyperglycemia is linked to subsequent formation of non-enzymatic glycosylation products, and further gives rise to advanced glycosylation end-products (AGEs). These AGEs increase cross-linking in collagen, tendons and ligaments, making these structures stiffer and weaker⁴. In addition, AGEs interact with their receptors on the surface of tenocytes and fibroblasts, thereby inducing inflammatory changes⁴. Furthermore, the unfavorable microvascular environment as a result of hyperglycemia occurs around the shoulder joint as well. The impaired circulation leads to tissue hypoxia, overproduction of free radicals, eventually leading to potential apoptosis. This collective damage might lead to joint tissue destruction and enhancement of degenerative changes.

Meanwhile, the cross-linking collagen accumulating in the shoulder capsule leads to joint stiffness and the chronic inflammatory process as a result of hyperglycemia, which might enhance the inflammation reaction in the synovium. Ultimately, these results contribute to capsular fibrosis of the shoulder joint. The mechanism might explain the association between frozen shoulder and diabetes. Notably, a similar pathogenetic mechanism occurs in the rotator cuff tendon, accompanied by tendon degradation, as well as structural and functional impairments. Weaker tendons develop as a result of AGEs, and the impaired circulation followed by inflammatory reaction tends to make the rotator cuff tendon vulnerable to injury. As a consequence, the degenerated rotator cuff tendon could tear more easily.

There is a consensus of opinion that poor blood sugar control and diabetes are related to microvascular and macrovascular complications of diabetes. However, no significant correlation of glycated hemoglobin and frozen shoulder has been reported to date. In a cross-sectional study, Thomas *et al.*¹ showed a significant association between duration of diabetes and frozen

shoulder, but there were no significant differences in the level of glycated hemoglobin or insulin use between diabetic patients with or without frozen shoulder. In the present study², one of the limitations was that the laboratory data were not available, so quantitative analysis of glycemic control and rotator cuff disease could not be carried out. However, using information on the administration of insulin (or not), it was possible to determine a potential association between poor glycemic control and the prevalence of rotator cuff disease based on the assumption that diabetes patients with poor blood glucose control require insulin injections. However, we found that diabetes patients had a higher hazard of rotator cuff diseases regardless of whether or not insulin was used. The issue as to whether enhancing glycemic control can reduce the chance of developing rotator cuff disease warrants further investigation. One of the interesting findings in this study was that the use of a statin was associated with a lower risk of developing rotator cuff disease in patients with hyperlipidemia (hyperlipidemia with statin use HR 1.16, hyperlipidemia without statin use HR 2.01)². Further studies are required to confirm the underlying mechanisms of this effect.

The anti-inflammatory effect of NSAID or steroid injection into the joint is a common practice for releasing pain and inflammation in the management of frozen shoulder and tendinitis of the rotator cuff. As a number of antidiabetic agents have been proven to have anti-inflammatory and anti-oxidative effects⁵, it is possible to find certain antidiabetic agents, such as metformin, might be useful in reducing shoulder disorders through various mechanisms.

In conclusion, shoulder disorders, such as frozen shoulder and rotator cuff disease, are commonly seen in patients with diabetes. Potential mechanisms include impaired microcirculation and non-enzymatic glycosylation processes around shoulder joint tissues and the synovium. Although frozen shoulder might be associated with the duration of diabetes, the association between metabolic control and the two aforementioned shoulder disorders has yet to be clearly shown. Further research is required to examine whether the use of certain antidiabetic agents and/or improved glycemic control could prevent or prolong the progression of rotator cuff disease and frozen shoulder in patients with diabetes.

DISCLOSURE

The authors declare no conflict of interest.

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