

SUMMARY POINTS

- Several musculoskeletal disorders occur exclusively or predominantly in people with diabetes.
- Increased collagen deposition limits joint function.
- Neuropathy can lead to musculoskeletal complaints.
- Some drugs, such as NSAIDs and steroids, may affect people with diabetes differently than others.

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Rheumatic Manifestations of Diabetes Mellitus

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When evaluating musculoskeletal complaints, physicians should consider the presence of diabetes because it may influence the management of these conditions.

There are several musculoskeletal disorders that exclusively or predominantly occur in people with diabetes (Table 1). Diabetes mellitus may influence the presentation, severity, and course of various musculoskeletal syndromes. Common therapies for the rheumatic diseases may differ in their effects in patients with diabetes compared to others.

Background

Diabetes mellitus is the most common endocrinopathy in the world. It exists in two forms that have traditionally been designated type I, or insulin-dependent diabetes mellitus (IDDM), and type II, or non-insulin-dependent diabetes mellitus (NIDDM).

IDDM occurs primarily in young people and is the result of an autoimmune attack on beta cells in the islets of Langerhans in the pancreas. NIDDM occurs predominantly in adults, is far more common, and is believed to result from relative insulin resistance. Both types result in hyperglycemia, glycosuria, and diffuse end-organ damage including nephropathy, retinopathy, neuropathy, and atherosclerosis.

The musculoskeletal syndromes occurring in diabetes may be divided into those related to increased collagen deposition resulting in limitation of normal joint function, those related to neuropathy, and other conditions.

Syndromes Related to Increased Collagen Deposition

The abnormal accumulation of collagen in skin and tendons leading to impairment of movement underlies several musculoskeletal complications of diabetes.

Nonenzymatic glycosylation of proteins (in this case collagen) and excessive deposition of these proteins in tissue has been proposed as an explanation for the development of these musculoskeletal syndromes. The amino groups of lysine residues often are irreversibly glycosylated, leading to increased cross-linking of collagen molecules and reduced breakdown of the protein. In addition, glycosylated collagen could possibly entrap other proteins and thus contribute to further skin thickening. The association with microvascular damage has led to speculation that ischemia may lead to a fibrotic reaction and contribute to the excessive thickening of tissue (1). It remains unclear why certain patients develop these clinical manifestations.

Cheiroarthropathy

Cheiroarthropathy is a syndrome of limited joint mobility, sometimes called the diabetic stiff hand syndrome. It is characterized by thickening and induration of the skin resulting in flexion contracture of the fingers (1). As a result, the patient cannot fully oppose the flexor surfaces of the fingers (prayer sign). Rarely, in more advanced cases, larger joints can be affected. The skin assumes a tight, waxy appearance that can be reminiscent of scleroderma. Histopathology reveals excess dermal collagen, but unlike in scleroderma, skin appendages are preserved and cross-linking of collagen can be abnormal (2).

Cheiroarthropathy has been reported to occur in up to 55% of patients with IDDM and in up to 76% of those with NIDDM (3). Its incidence correlates to number of years of

diabetes. There is also a positive association with the presence of microvascular disease of the kidney and retina. Patients often present with stiffness and discomfort of the fingers. Therapy usually includes analgesics or anti-inflammatories, but response is often disappointing. Good glycemic control may slow or halt, but cannot reverse, the process.

Frozen Shoulder

Frozen shoulder or adhesive capsulitis of the shoulders is a relatively common condition involving pain and restriction on both active and passive shoulder movement. It occurs significantly more commonly in people with diabetes than in the general population (4). It is not clear whether the complication is related to glycemic control.

Frozen shoulder can be quite debilitating and long-lasting (1-2 years). Therapies include physical therapy, analgesics, glucocorticoid injections, surgical capsulotomy, and manipulation under anesthesia. Response to therapy may be poor though eventual spontaneous resolution is the rule in patients with and without diabetes (5). Because spontaneous resolution usually occurs, conservative treatment with analgesics and physical therapy should be emphasized.

Flexor Tenosynovitis

Flexor tenosynovitis is an inflammatory and fibrotic process involving the flexor tendons of the fingers often resulting in “trigger finger.” The involved finger, when flexed, “locks” in place. Extension of the finger is painful and may be accompanied by an audible snap. Often a painful nodular area can be palpated along the flexor tendon. Local glucocorticoid injection is often helpful, although surgery is necessary on occasion.

Flexor tenosynovitis is more common in people with diabetes (6). It has been described as an early complication, sometimes before the onset of frank diabetes. Some have suggested glucose tolerance testing in nondiabetics with the syndrome.

Dupuytren's Contracture

Dupuytren's contractures present with palmar fascial thickening leading to skin puckering and flexion contracture of the third through fifth fingers. It is most common in middle-aged and older men and may be associated with excessive alcohol intake as well as diabetes. Occasional response to local injection has been reported. Surgery may be tried, but it is complex, difficult, and fraught with complications (7).

Syndromes Related to Neuropathy

Long-standing diabetes is frequently complicated by peripheral neuropathy, particularly involving the sensory nerves. This may predispose to several musculoskeletal syndromes.

Charcot's Arthropathy

Charcot's arthropathy is a destructive process predominantly involving the foot and ankle in people with long-standing diabetes and peripheral neuropathy (8). Other terms used to describe the syndrome include diabetic osteopathy, neurogenic osteopathy, and diabetic osteolysis. (There is no consensus regarding nomenclature of these syndromes. Some would classify diabetic osteopathy separately from neuropathic or Charcot's joints. They are considered together here for simplicity's sake and due to similar pathophysiology.)

Charcot's arthropathy is similar or identical to the process first described in the nineteenth century in patients with other causes of neuropathy, predominantly syphilis. Peripheral sensory neuropathy leading to relative insensitivity to pain, and to multiple traumatic events, is the underlying cause. A fracture, often undetected at the time, may incite the process. Bony destruction often begins in the medial portion of the midfoot and then may progress laterally and posteriorly (9). Progressive loss of the arch may sometimes occur, resulting in a “rocker-bottom” deformity. Less commonly, dorsal protrusion of the foot may occur. These deformities can lead to increased mechanical pressure and resultant ulcerations and secondary infections.

TABLE 1

Musculoskeletal Disorders Found Predominantly in People with Diabetes

1. Cheiroarthropathy (diabetic stiff hand syndrome)
2. Frozen shoulder
3. Flexor tenosynovitis
4. Dupuytren's contracture
5. Charcot's arthropathy
6. Reflex sympathetic dystrophy (complex regional pain syndrome)
7. Diffuse idiopathic skeletal hyperostosis

Neuropathy and chronic trauma are crucial to this process, as demonstrated by the occurrence of identical processes with other causes of nerve damage such as syringomyelia resulting in shoulder damage. Nevertheless other factors including pre-existing osteopenia, vascular disease, and shedding of calcium pyrophosphate crystals also may play a role (10).

Protecting the foot through casting and by avoiding weight bearing is helpful and by itself can result in healing and reformation of bone. Charcot's arthropathy usually occurs after many years of diabetes but may be a presenting complaint.

Reflex Sympathetic Dystrophy

Reflex sympathetic dystrophy (RSD), also known as complex regional pain syndrome (CRPS), is a poorly understood pain syndrome that is more common in people with diabetes than in the general population (11). Some have argued that the dysautonomia of diabetes is necessary for the full expression of the syndrome (12).

RSD frequently follows trauma or other painful conditions (eg, radiculopathy). Rather than recovering from a painful event, a localized area begins to demonstrate allodynia (when ordinarily painless stimuli are experienced as painful) with temperature dysregulation and vasomotor abnormalities (eg, flushing or blanching). Often a temperature difference can be discerned between the affected and unaffected limb, and sweating and color differ-

ences occur. The patient tends to protect the painful area and avoid using the limb.

Late-stage changes include muscle atrophy, patchy osteoporosis, and markedly diminished function. At this stage radiographs may be diagnostic, showing patchy osteoporosis. At earlier stages there may be characteristic abnormalities (increased uptake) on bone scanning. Treatment includes analgesia, physical therapy, and occasionally sympathetic blocks. Bisphosphonates have also been said to be helpful (13).

Other Syndromes

People with diabetes may be more prone to osteoarthritis than others (14). Animal models of diabetes demonstrate increased destruction of articular cartilage (15) and epidemiologic studies demonstrate an association (16). The strong association between obesity and NIDDM, however, makes interpretation of the data difficult.

Osteopenia related to increased osteoclastic activity and decreased osteogenesis occurs in IDDM (17). Several mechanisms may underlie this decreased bone density. Glycosuria leading to hypercalciuria may contribute. Alterations in vitamin D and calcium metabolism have also been demonstrated. Hydroxyproline excretion, a marker of bone resorption, is increased in IDDM. Similar studies of NIDDM patients are conflicting (18).

Diffuse idiopathic skeletal hyperostosis (DISH) is a hypertrophic process of bone that occurs with increased incidence in diabetes, especially NIDDM. The spine is most commonly affected, with calcification of the anterior longitudinal ligament, giving the appearance of flowing calcification connecting the anterior aspects of the vertebrae. In contrast with the seronegative spondyloarthropathies, sacroiliac joints are preserved. Often the diagnosis is suggested by a radiograph on an asymptomatic patient. Back pain and stiffness can occur and, much more rarely, hyperostosis of the cervical spine, which rarely can lead to dysphagia or myelopathy. Hyperostosis has also been described at many extraspinal locations such as the pelvis, foot, and elbow, and may also result in pain and stiffness (19).

People with diabetes are more prone to infections, and this susceptibility extends to musculoskeletal infections including septic arthritis and pyomyositis. Long-standing diabetes, usually with severe renal disease, can be associated with “diabetic muscle infarction” (20). This is a very painful syndrome – usually involving the thighs – that often requires management with narcotic analgesics.

Other musculoskeletal syndromes that the literature indicates may be associated with diabetes include gout, pseudogout, carpal tunnel syndrome, and rheumatoid arthritis. It is difficult to determine if there truly is an association with diabetes or if they are simply common but unrelated conditions.

Influences on Treatment

Therapeutic decisions in patients with musculoskeletal complaints must take into account the presence of diabetes.

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in musculoskeletal conditions. Their most common side effect is gastrointestinal tract mucosal irritation, which can lead to ulceration and bleeding, which may occur more often in patients with concomitant medical conditions including diabetes.

The kidney also can be affected by NSAIDs. The most common renal problems are due to decreased glomerular filtration from prostaglandin inhibition caused by NSAIDs including COX-2 inhibitors in those with preexisting renal insufficiency. Because diabetes is a leading cause of renal insufficiency in the Western world, its presence should be considered before NSAIDs are prescribed.

Glucocorticoids are commonly used for their anti-inflammatory and immunosuppressive properties in the rheumatic diseases. The use of such therapy is substantially more difficult in people with diabetes due to increases in serum glucose levels in diabetes. If glucocorticoid therapy cannot be avoided, doses of insulin or oral hypoglycemics are likely to require adjusting, and monitoring of serum glucose must be frequent. Glucocorticoids

are also well known to cause NIDDM in previously unaffected patients. This is especially common in overweight patients or those with a family history of NIDDM.

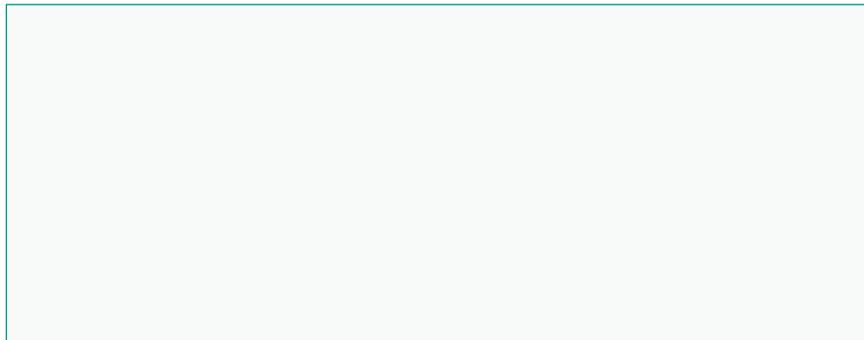
Summary

The presence of diabetes mellitus must be recognized when evaluating and treating patients with musculoskeletal complaints. The spectrum of rheumatic disease is different in people with diabetes, the course of the disease may be altered, and certain therapies may be substantially more hazardous.

References

1. Kapoor A, Sibbitt WL. Contractures in diabetes mellitus: the syndrome of limited joint mobility. *Semin Arthritis Rheum* 1989;18:168-80.
2. Gonzalez T, Gantes M, Diaz-Flores L. Digital sclerosis and juvenile diabetes. *Arthritis Rheum* 1984;27:478-9.
3. Starkman HS, Gleason RE, Rand LI, et al. Limited joint mobility of the hand in patients with diabetes mellitus: relation to chronic complications. *Ann Rheum Dis* 1986;45:130-5.
4. Fisher L, Kurtz A, Shipley M. Association between cheiroarthropathy and frozen shoulder in patients with insulin-dependent diabetes mellitus. *Br J Rheumatol* 1986;25:141-6.
5. Thornhill TS. Shoulder pain. In Kelly WN, Harris ED, Ruddy S, Sledge CM editors. *Textbook of Rheumatology*. Philadelphia: WB Saunders; 1997: 431-2.
6. Leden I, Jonsson G, Larsen S, et al. Flexor tenosynovitis: a risk indicator of abnormal glucose tolerance. *Scand J Rheumatol* 1985;14:293-7.
7. Schneider LH, Hankin FM, Eisenberg T. Surgery of Dupuytren's disease: a review of the open palm method. *J Hand Surg* 1986;23-7.
8. Sinha S, Munichoodappa CS, Kozak GP. Neuro-arthropathy (Charcot joints) in diabetes mellitus. *Medicine* 1972;51:191-210.
9. Griffith J, Davies AM, Close CF, et al. Organized chaos? Computed tomographic evaluation of the neuropathic diabetic foot. *Br J Radiol* 1995;68:27-33.
10. Jacobelli S, McCarty D J, Silcox DC, et al. Calcium pyrophosphate dihydrate crystal deposition in neuropathic joints. Four cases of polyarticular involvement. *Ann Intern Med* 1973;79:340-7.
11. Doury P, Dequeker J. Algodystrophy/reflex sympathetic dystrophy syndrome. In: Klippel JP, Dieppe P, editors. *Rheumatology*. New York: Mosby; 1994. p. 7.38.1-7.
12. McGuire JL, Lambert RE. Arthropathies associated with endocrine disorders. In Kelley WN, Harris ED, Ruddy S, Sledge CM editors. *Textbook of Rheumatology*. Philadelphia: WB Saunders; 1997. p. 1500-2.

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13. Adami S, Fossaluzza V, Gatti D et al. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Ann Rheum Dis* 1997;56:201-4.
14. Cimmino MA, Cutolo M. Plasma glucose concentration in symptomatic osteoarthritis: a clinical and epidemiologic survey. *Clin Exp Rheum* 1990;8:251-7.
15. Silberberg R, Gerritsen G, Hasler M. Articular cartilage of diabetic Chinese hamsters. *Arch Pathol Lab Med* 1976;100:50-4.
16. Caterson B, Baker JR, Christner JE et al. Diabetes and osteoarthritis. *Ala J Med Sci* 1980;17:292-9.
17. Auwerx J, Dequeker J, Bouillon R, et al. Mineral metabolism and bone mass at peripheral and axial skeleton in diabetes mellitus. *Diabetes* 1988;37:8-12.
18. Weinstock RS, Goland RS, Shane E, et al. Bone mineral density in women with type II diabetes mellitus. *J Bone Min Res* 1989;4:97-101.
19. Resnick D, Shaul SR, Robins JR. Diffuse idiopathic skeletal hyperostosis (DISH): Forestier's disease with extraspinal manifestations. *Radiology* 1975;115:513-24.
20. Grigoriadis E, Fam AG, Starok M, et al. Skeletal muscle infarction in diabetes mellitus. *J Rheumatol* 2000;27:1063-8.

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