Musculoskeletal Manifestations of Diabetes Mellitus

A Review for the practicing radiologist and radiologist in training, with emphasis on clinical presentation, pathogenesis, and imaging appearance.

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Objectives

- To review and highlight the musculoskeletal manifestations of diabetes mellitus (DM), including osteomyelitis, neuropathic arthropathy, diabetic myonecrosis, and dialysis-associated spondyloarthropathy.
- The imaging appearance of these various entities will be highlighted at commonly encountered locations, including the spine, thigh, and foot.
- To provide a useful and relevant review of the clinical presentation and pathogenesis of the various DM-related entities.
- Emphasis will be placed on features that may help distinguish these entities from other similar appearing processes, with the goal of avoiding unnecessary patient imaging, intervention, and morbidity.

Pathophysiology of Diabetes¹

- Diabetes can be characterized as hyperglycemia resulting from β-cell destruction or dysfunction
  - Type I – immune mediated destruction of β-cells
  - Type II – glucose specific insulin secretory defects
- Results from a combination of genetic and environmental factors
- Advanced glycation end-products (AGE)⁴
  - Product of nonglycemic glycation and oxidation
  - AGE are antigenic and induce inflammation
  - Contribute to formation of damaging reactive oxygen/nitrogen species
  - Accumulate in extracellular matrix of tissues and cross link intracellular and extracellular proteins
- Nervous system damage is seen in up to 70% of diabetes patients
Epidemiology of Diabetes Mellitus

- The diabetes epidemic
  - In 2015 in the United States, 30.3 million people (9.4% of the population) had diabetes
    - 7.2 million were undiagnosed
    - 84.1 million people >18yo had prediabetes
      - Elevated blood glucose levels but below the diagnostic level for DM
  - 1.5 million people are diagnosed with diabetes a year
  - 7th leading cause of death in US in 2015

Economic Burden of Diabetes

- Diabetic care accounts for up to 1 in 4 dollars spent on healthcare
  - $327,000,000,000: Total estimated cost of diagnosed diabetes
    - $237,000,000,000: direct medical costs
    - $90,000,000,000: reduced productivity
  - On average, patients with diabetes have 2.3x higher medical expenses
  - From 2012 to 2017, costs related to diabetes increased by 26%
Musculoskeletal Manifestations of Diabetes\textsuperscript{5,6}

- Osteomyelitis
- Neuropathic Osteoarthropathy “Charcot Foot”
- Infected Neuropathic Osteoarthropathy
- Diabetes Associated Spondyloarthropathy
- Diabetic muscle ischemia/myonecrosis
- Pyogenic Spondylodiscitis
- Neuropathic Spine “Charcot Spine”
- Diffuse idiopathic skeletal hyperostosis
- Inflammatory arthritides/Gout
- Osteoporosis
- Fibrosing syndromes
  - Adhesive capsulitis of the shoulder
  - Carpal tunnel
  - Dupuytren’s contracture
- Complex regional pain syndrome\textsuperscript{Bolded} items will be discussed in further detail

Diabetes Related Pedal Disorders

- Neuropathy results in altered biomechanics and proprioception as well as anhidrosis\textsuperscript{3}
  - Leads to dry skin and callous formation with skin breakdown/ulceration predisposing to infection\textsuperscript{3}
  - ~15\% of diabetics will develop neuropathic arthropathy\textsuperscript{7}
  - ~15\% of diabetics will develop osteomyelitis\textsuperscript{7}
- Limb hyperemia and bone resorption arise from loss of sympathetic neuroregulation\textsuperscript{6}
  - Leads to neuropathic destruction
- Annual incidence of nontraumatic limb amputation is 2.1-13.7 per 1000\textsuperscript{6}
  - High 5-year mortality following diabetes-related lower extremity amputation (30\%-80\%)\textsuperscript{6}
- 25\% lifetime chance for foot ulceration\textsuperscript{4}
- Ulceration often occurs at pressure points\textsuperscript{1,3}
  - Plantar aspect 1st metatarsophalangeal joint or 5th metatarsal head
  - Tip of distal phalanx of first toe
  - Calcaneus
- Midfoot ulcers are rare in the absence of underlying osteoarthropathy
- Dorsal aspect of toes from clawtoe formation
  - Due to motor neuropathy of intrinsic muscles of foot
Osteomyelitis – Radiographic Findings

- Infection of bone marrow
- Osteomyelitis in diabetes almost always arises from contiguous spread from a skin ulcer/wound.\(^6,13\)
- Radiographic features\(^6\)
  - Often lag behind clinical findings 10-20 days\(^6\)
  - Can repeat in 2-4 weeks\(^6\)
  - Periostitis and cortical destruction\(^6,7\)
  - Weight bearing films can help reveal amputation sites, foreign body, soft tissue gas, and malalignment\(^6\)
- Lateral X-ray of the calcaneus: Large soft tissue defect involving the left heel with underlying cortical erosion/defect of the calcaneus.

Osteomyelitis – MRI Findings\(^6,7,13\)

- Bone marrow edema with adjacent soft tissue ulceration or abscess
- T1 weighted sequences: diffuse low signal
- Fluid sensitive sequences (T2, STIR): hypointense marrow signal corresponding to hypointense T1 signal
- Contrast enhanced sequences: enhancing areas of marrow represent viable areas of tissue; non-enhancing areas represent necrotic non-viable tissue
- Adjacent soft tissue abnormality such as ulcer, sinus tract, or abscess are usually seen
  - Lack of adjacent soft tissue infective process renders osteomyelitis less likely
- Sagittal T1-weighted (left) and STIR (right): A large soft tissue defect is seen along the posterior aspect of the calcaneus with associated soft tissue edema. A large defect is seen along the posterior/plantar aspect of the calcaneus with associated hypointense T1 and hyperintense STIR signal.
Osteomyelitis – Differential Diagnoses

- Reactive marrow change from adjacent soft tissue or cortical infection
- Areas of T2/STIR hyperintensity without corresponding T1 hypointense signal
  - Regardless of enhancing characteristics
- Acute/early neuropathic arthropathy
  - Discussed later
  - Primarily articular
  - Often lacks adjacent soft tissue abnormality

Sagittal and coronal T1 weighted MRI (upper left, lower left) and sagittal and coronal STIR MRI (upper right, lower right) demonstrate bone marrow edema involving the proximal phalanx of the great toe without convincing bone marrow replacement on T1 sequences. There is surrounding circumferential soft tissue edema at the great toe and extending into the midfoot. The patient had recently undergone an amputation of the first distal phalanx and findings were attributed to reactive osteitis.

Neuropathic Arthropathy

- Neuropathic changes results in loss of proprioception and pain
  - Leads to unrecognized trauma to weightbearing joints
- Autonomic dysregulation causes hyperemia leading to weakening of bone
- Majority of cases occur at tarsometatarsal joints
  - Also occurs at subtalar, intertarsal, and ankle joints
- Acute phase: soft tissue swelling, erythema, fluid collections, effusions, marrow abnormalities
  - Leadographs are often negative
- Chronic phase: foot deformity without soft tissue edema and little/no bone marrow edema
  - “6 D’s”
    - Increased Density
    - Joint Distension
    - Articular Disorganization
    - Osteous Debris
    - Destruction
    - Joint Dislocation
  - Leads to rocker bottom deformity of foot
Neuropathic Arthropathy – Radiographic Findings

- Acute phase: often radiographically occult\(^1\)\(^3\)
- Chronic phase: “6 D’s”\(^7\)
  - Increased Density
  - Joint Distension
  - Articular Disorganization
  - Osseous Debris
  - Destruction
  - Joint Dislocation

Frontal and lateral radiographs of the foot demonstrate erosive and destructive changes of the midfoot joints with associated osseous debris and disorganization.

Neuropathic Arthropathy – CT Findings

- CT findings:
  - Similar to radiographic findings
  - Example case (images on right)

Multiplanar CT images of the foot (right) show extensive osseous fragmentation and periarticular destruction with diffuse displacement and disorganization of the metatarsal joints.
Neuropathic Arthropathy – MRI Findings

**Acute phase:**
- T1 weighted sequences: multiple foci of hypointense marrow signal
- Fluid weighted sequences (T2/STIR): multiple foci of hyperintense marrow signal
- Extensive soft tissue edema and enhancement *WITHOUT* ulceration or extension to skin
- Contrast enhanced sequences: periarticular and subchondral enhancement
- Subchondral cysts, articular erosions, joint effusion

**Chronic phase:**
- Decreased marrow signal on all sequences due to osteosclerosis
- Bony deformity, bone fragmentation, joint effusion, well defined subchondral cysts, debris, intra-articular bodies

Sagittal T1 weighted and STIR MRI of the ankle (top) and axial T1 weighted and STIR MRI (bottom) demonstrate diffuse low T1/STIR signal involving the bones of the midfoot and at the base of the second and third metatarsals. There is some fragmentation and dislocation involving the intermediate and lateral cuneiforms. Some debris is noted with associated joint effusion and synovitis within the midfoot. No soft tissue ulceration or source for contiguous spread is identified.

Osteomyelitis vs Neuropathic joint

**Osteomyelitis**
- T1 sequence: **DIFFUSE** decreased signal
- Location: points of pressure
- Adjacent soft tissue ulcer/wound

**Acute neuropathic osteoarthropathy**
- T1 sequence: Periarticular/subchondral decreased signal
- Location: tarsometatarsal and metatarsophalangeal joints
- Often lacks adjacent soft tissue ulceration or sinus tract
- Multiple bone and joint involvement
Infected Neuropathic Arthropathy

- In later stages of neuropathic osteoarthropathy, destructive changes can lead to development of rocker bottom deformity.
  - This results in atrophy in the pressure points of the foot and can lead to development of ulceration and skin defects in unusual locations.
  - Osteomyelitis in this setting most commonly affects the cuboid bone.
- Soft tissues signs of superimposed infection include:
  - Development of sinus tract
  - Replacement of adjacent soft tissue fat
  - Presence of adjacent soft tissue fluid collections
- Soft tissue signs that are NOT helpful:
  - Skin ulceration
  - Soft tissue enhancement
  - Rim-like enhancement of periarticular fluid collections
- Osteous signs of superimposed infection include:
  - Disappearance of previously seen subchondral cysts and intra-articular bodies
  - Extensive or diffuse bone marrow edema
    - Vs. the periarticular predilection in osteoarthropathy
  - “Ghost sign”
    - “Disappearance” of bone on T1 weighted sequences that “re-appear” on T2 weighted sequences or post-contrast sequences

Infected Neuropathic Arthropathy

Lateral (above) and oblique (right) radiographs of the foot reveal soft tissue ulcers within the plantar midfoot and heel with diffuse soft tissue swelling. There is advanced neuropathic arthritis with severe osteopenia and suspicion of localized destruction of the lateral midfoot concerning for osteomyelitis.
Infected Neuropathic Arthropathy

Sagittal T1 weighted (left), STIR (right), and T1 fat saturated post-contrast (bottom) MRI images demonstrate frank disorganization of the midfoot/hindfoot consistent with underlying neuropathic arthropathy. Areas of frank homogeneous T1 marrow replacement and enhancement in the proximal one half of the remaining fifth metatarsal (black arrows) and a small portion of the remaining distal cuboid bone (white arrow) are suspicious for multifocal osteomyelitis.

There are also joint effusions/ fluid collections at the tibiotalar and subtalar joints extending beyond the expected typical confines of the joint space with extensive surrounding soft tissue edema and enhancement raising concern for septic arthritis/soft tissue abscess.

Diabetic Muscle Ischemia (DMI)

- "Diabetic myonecrosis"
- Poorly controlled and long standing diabetes6,7
  - Often have associated end-organ damage
- Pathophysiology6:
  - Thought to be due to microangiopathy
  - Muscle necrosis and edema with fibrous blockage of vessels
- Most commonly affects thigh (71.2%) followed by calf (15.3%)11
  - Often spares rectus femoris and sartorius9
  - Often noncontiguous muscle group involvement6
  - Bilateral in 8.4% of cases11
- Abrupt onset of severe pain and swelling6,7
  - Lacks leukocytosis6
  - Fever is present in ~10%9
- Usually self-limiting with good short term prognosis:
  - Indicates poor long-term prognosis due to vascular compromise
  - Recurrence rate of 40% with 2-year mortality of 10%
- Biopsy is reserved for atypical patients due to risk of hemorrhage, infections, and poor wound healing11
- Treatment is conservative with glycemic control, analgesics, and antiplatelet therapy:
  - Surgery is associated with longer recovery and increased mortality.
Diabetic Muscle Ischemia – CT Findings\textsuperscript{10, 11}

- Ill-defined areas of hypoattenuation within the thigh or calf muscles
- Bulky appearance of the muscles with patchy enhancement
- Edema and stranding within the subcutaneous fat

Axial (left), sagittal (middle), and coronal (right) CT images of the right lower extremity demonstrate enlargement and hypodensity of the peroneal muscles along the entire leg with bulging of the fascia superficial to the musculature and deep to the subcutaneous tissues. A few internal foci of enhancement are seen within the muscle with strandy subcutaneous edema around the leg in a reticular pattern with more confluent regions along the anterior aspect.

Diabetic Muscle Ischemia – MRI Findings

- Preferred modality
- Muscle enlargement and edema
  - Loss of intermuscular septa on T1-weighted sequences\textsuperscript{7}
- Fascial edema
- Areas of T1-weighted sequence hyperintensity suggest hemorrhagic component\textsuperscript{7}
- Post-contrast:
  - Pattern 1: Muscle enhancement with internal regions of hypo/non-enhancement\textsuperscript{6}
  - Pattern 2: Linear streaks of enhancement passing through a non-enhancing central zone within an enhancing muscle\textsuperscript{7}

Axial and coronal T1 weighted images (top) and axial and coronal STIR images (bottom) demonstrate diffuse subcutaneous edematous changes, present most prominent on the left. There is diffuse swelling of the visualized proximal left thigh muscular primarily involving the adductor muscles, visualized quadriiceps muscles, and distal left ilopsoas muscle (not shown). Abnormal signal is also seen in the right adductor musculature, portions of the anterior right thigh musculature, portions of the gluteal musculature bilaterally, tensor (not shown), and obturator internus muscles.
Diabetic Muscle Ischemia – Differential Diagnosis

- **Infectious myositis**
  - Often febrile with leukocytosis, bacteremia and elevated inflammatory markers
  - Smooth walled intramuscular abscesses with rim enhancement
  - As opposed to the heterogenous streaky enhancement of DMI
  - Often requires antibiotics and drainage

- **Inflammatory myositis**
  - Often slow onset with progressive proximal muscle weakness
  - Findings are bilateral and symmetric
  - Often have associated skin lesions

Axial and sagittal T1 weighted MRI (upper left, lower left), axial fluid sensitive sequence MRI (upper right), and coronal STIR MRI (lower right) demonstrate significant and diffuse abnormal increased T2/STIR signal throughout the left quadriceps, hamstring, and partially visualized gluteus musculature. There is also mild to moderate soft tissue edema and subcutaneous edema. Intramuscular and superficial fascial fluid is most prominent anteriorly. Patient had a known history of polymyositis.

Dialysis-associated Spondyloarthropathy

- “Destructive Spondyloarthropathy”
- In patients undergoing long term (>2years) hemodialysis for chronic renal disease
- Due to β2-microglobulin (amyloid) deposition, which occurs in both the appendicular and axial skeleton
  - Some studies have shown association with amyloid associated arthropathy of hands and wrists
  - Prevalence of 5-23.5% of patients on dialysis
Dialysis-associated Spondyloarthropathy

- Predilection for the cervical spine
  - Also involves the craniocervical junction and thoracolumbar spine
- Can affect single or multiple levels, and may be continuous or skip levels
- Serum markers include elevated levels of antibodies to β2-macroglobulin
  - Definitive diagnosis may require percutaneous biopsy

Characterized by:
- Intervertebral disk space loss
- Extensive vertebral endplate erosions and sclerosis
- Minimal or no endplate osteophyte formation
- Facet involvement, subcortical cystic change, Schmorl’s node formation, and lack of associated soft tissue mass are also features

Dialysis-associated Spondyloarthropathy – Radiographic Findings

- Narrowing/loss of the intervertebral disc space
- Endplate erosions or subcortical bone resorption
  - +/- cystic changes
- Subcortical sclerosis
- Minimal/no endplate osteophyte formation
- Early: erosions of the anterior corners of the vertebral body may mimic ankylosing spondylitis
- Advanced: vertebral fracture, subluxation, spondylolisthesis

AP and lateral radiographs of the lumbosacral spine demonstrate diffuse skeletal sclerosis, compatible with renal osteodystrophy. Pronounced destructive/erasive changes at the adjoining endplates of T12-L1 vertebra are seen.
Dialysis-associated Spondyloarthropathy – CT Findings

- Similar to radiographic findings
  - Loss of intervertebral disc space
  - Endplate erosions and sclerosis
  - Minimal/no osteophyte formation
- CT better depicts subcortical cystic changes
- Provides better evaluation of extent of involvement
- CT helps assess for associated soft tissue abnormalities (abscess) to help distinguish between infective spondylodiscitis

Sagittal bone kernel (left), sagittal soft tissue kernel (middle), and coronal bone kernel (right) CT shows mild generalized sclerosis with disc space narrowing at C4-C5 and C6-C7 and multiple subchondral erosions in the adjoining vertebral endplates. The rest of the intervertebral disc spaces appear maintained.

Dialysis-associated Spondyloarthropathy – MRI Findings

- T1-weighted sequences
  - Hypointense signal involving the disc and endplates
- T2-weighted sequences
  - Variable signal involving disc and endplates
  - Most commonly the disc space is T2 hypointense
    - Helps distinguish between infection
- Enhancement
  - Variable
  - Some studies suggest enhancement may be related to reactive inflammation surrounding deposits of amyloid

Motion limited sagittal T1 and STIR MRI images of the cervical spine show subcortical marrow edema at the C5-C6-C7 level with intermediate T2 signal involving the disc (arrow). Corresponding CT (not shown) showed endplate sclerosis and erosive changes. Primary consideration was given to non-infectious/dialysis-associated spondyloarthropathy.
Dialysis-associated Spondyloarthropathy – Differential Diagnoses

- Infection
  - Often clinically evident with fevers and elevated inflammatory markers
  - Key feature is T2 hyperintense signal and enhancement of the disc
  - Can also have paraspinal/epidural abscess or phlegmon
- Degenerative disc disease
  - Often have associated osteophyte formation
- Ankylosing spondylitis
  - Anterior vertebral body corner erosions are seen in both entities

Sagittal T1 (left), T2 (middle), and STIR (right) MRI images demonstrate changes of early discitis/osteomyelitis at L4-5 with abnormal fluid signal involving the L4-5 disc and adjacent endplates.

References

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