Pathophysiology of Diabetes Mellitus in the Foot and Ankle

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Disclosure

I have no conflict of interest to disclose.
Outline

• Scope of the Problem
• Pathophysiology
  – Neuropathy
  – Vasculopathy
  – Infection
• Amputations
• Charcot Arthropathy

Scope of the problem

• 16 to 18 million Americans (5% of population) have diabetes mellitus (DM)
• From 1990 through 2010, the number of new cases of diagnosed DM tripled
• By 2025 21.9 million Americans will have diabetes
• 285 million patients with diabetes worldwide (2010), 439M by 2030
Scope of the problem

• Medical expenses for a person with DM >2x
  – $116B direct medical care costs
  – $58B in costs due to disability, productivity loss, and premature death
• International Diabetes Federation:
  – Cost by 2030: $490B worldwide

Scope of the problem

• Diabetics are living longer
• 25% of all diabetic-related hospitalizations are foot infections
• Increased risk for morbidity when undergoing surgery
Pathophysiology

- **Neuropathy**
- Vasculopathy
- Infection

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**Peripheral Neuropathy**

- Most common disabling chronic complication in diabetes
- Effects up to 60% with diabetes
- More prevalent with increasing age and duration of DM
- Irreversible
## Incidence

- 30% on gross clinical exam
- 20% of patients having diabetes mellitus > 10 years
- 50% of patients having diabetes mellitus > 15 years

## Physical Presentation

- **Insensitivity**
  - Diminished pain, temperature, touch, and vibration
- **Pain**
  - burning, tingling, radiating pain beginning at the toes and progressing Motor weakness and deformity
- **Motor dysfunction and deformity**
  - imbalance between the flexor and exterior mechanisms
  - clawing toes and increased prominence of metatarsals heads.
Etiology

- Unknown
- Not caused by changed in local nerve vascular supply
- No relationship to metabolic requirements of disease but rather to control of disease (NIH 10 year study reported close glucose control reduced neuropathy by 60%)

Sensory involvement

- Insensitivity
  - primary cause of unrecognized injury or ulceration
- Pain
  - burning, often worse at nighttime, diminishes over time
- Stocking (and glove) distribution
  - the further distal the greater the loss of feeling
Diagnostic aids

- Pinprick (crude)
- Vibratory
- Semmes-Weinstein monofilament testing
  - Inexpensive
    - 5.07 filament threshold for protective sensation, 90% of diabetics

Motor involvement

- Less severe than sensory
- imbalance between the flexor and exterior mechanisms (Intrinsic muscle dysfunction)
  - Claw toes
  - increased prominence of metatarsals heads
  - Bunions
- Mononeuropathy
  - Common peroneal nerve→ foot drop
Autonomic Involvement

- Thermocontrol, glandular control
- Loss of normal sweating and skin temperature regulation
- Dry, cracked skin → portals for bacteria, fungus
- Nail deformities
Treatment

- EDUCATION

Patients with severe neuropathy can experience severe pain
- Tricyclic antidepressants
- GABA-B agonists (Baclofen)
- Anticonvulsants/ neuromodulators
  - Gabapentin
  - Pregabalin
  - Phenytoin
  - Carbamazepine
Treatment

• Protective
  – Identify patients at risk
  – Close observation of feet
  – Appropriate shoe wear, orthotics
    • Medicare will reimburse
  – Skin care

Vasculopathy
Vaculopathy

• At least 4x that of non-diabetic individuals
  – increases with age and duration of diabetes
  – 8% of adult diabetics at diagnosis
  – 45% after 20 years

• Peripheral vascular disease is more prevalent, occurs at an earlier age, is more diffuse, accelerates faster, and is more extensive

Vasculopathy

• Large and small vessel disease
  – blockages of femoropopliteal and aortoiliac vessels → chronic ischemia.
  – In combination with digital artery disease → ulceration and gangrene
Symptoms

- Ischemia (occlusive disease)
  - Beware of painful toes with innocuous-appearing infection
  - Intermittent claudication, activity related
  - Rest pain
  - Usually at most distal site
  - Common in midfoot
  - Worse with elevation
  - Night pain

Physical examination

- Assess:
  - Color
  - Temperature
  - Pules
Acute occlusion

- Marked color change (blue!)
- Decreased temperature
- Can lead to wet gangrene
- Must rule out deep abscess, endocarditis, etc

Chronic occlusion

- No palpable pulses
- Dry gangrene (mummification)
- No hair growth, dystrophic nails
- Atrophy of tissues
- Amputate!
Ulceration 2/2 ischemia

- Toes
- Must differentiate from neuropathic and venous ulcers
- Punctate (cigarette burns)

Diagnosis

- Pulses!
  - If you can feel pulses, ulcer likely not vascular
Diagnosis

• Arterial doppler study
  – Noninvasive, inexpensive
  – Pulse volume recordings
  – Toe pressures
  – A/B index (ABI)
**Significance of ABI**

- Normal: 0.91 to 1.30,
- >1.3 representing poorly compressible vessels
  - Medial artery calcinosis $\rightarrow$ arterial wall stiffness $\rightarrow$ false elevation of systolic pressure
  - So if normal
    - check toe pressure
    - Check waveforms
      - Triphasic: normal
      - Monophasic: noncompressible
- 8x (700%) increased risk of lower extremity amputation in patients with an ABI $\leq$ 0.90

**Arterial studies**

- Healing potential is favorable if:
  - A/B index > 0.45
  - Toe pressure > 40-50 mm Hg
  - A/B index > 1.3 – calcification
Transcutaneous PO$_2$ study

- Noninvasive, probe over metatarsal
- Not falsified by calcification of vessel
- Can be lowered by presence of infection
- Operator dependent

Transcutaneous PO$_2$ study

- Healing potential is favorable if:
  - $>40$mmHg

- Healing rates correlated w TCpO2:
  - 50%: 1-19mmHg
  - 75%: 20-29 mmHg
  - 92%: 30mmHg
Arteriogram

- Invasive, expensive
- Gold standard to tell level of occlusion

Arteriogram

- Has its complications
  - Renal toxicity
  - Pseudoaneurysm
  - Allergic reaction to dye
Vasculopathy treatment

• Talk to your vascular surgeon
  – Revascularization/angioplasty procedure
    • Can help covert BKA to a more distal procedure
  – Consult before any amputation or big Charcot reconstruction

Treatment

• Hypobaric treatment
  – Costly
  – Mixed results
Infection

General principles

• Tolerate infection poorly
• Altered chemotaxis of polys
• Decreased phagocytosis and mobilization of polys

• Bacterial or fungal: polymicrobial
  – Anaerobe especially
  – Rarely gas gangrene
    • True gas gangrene demonstrates gram-positive rods on the Gram stain
General principles

- Need deep cultures
- Swab cultures of ulcer/sinus
  - 60% correlative to deep culture
- Typical triad of bugs:
  - G-positive cocci (e.g., staphylococci, group B streptococci, and enterococci)
  - G-negative aerobic rods (e.g., *Escherichia coli*, *Enterobacter*, *Proteus*, and *Pseudomonas*),
  - Anaerobes (*Bacteroides fragilis* and other *Bacteroides*, *Clostridium*, and peptostreptococci)

Physical examination

- Hot, swollen and red!!!
  - Not always painful

- Cellulitis vs. abscess vs. Charcot
  - Elevate and observe for a few minutes to distinguish erythema vs. dependent rubor (Charcot)
  - IV antibiotics may confuse the issue
Physical examination

• Abscess
  – 1\textsuperscript{st} webspace/deep plantar space most common
  – Look for entry portal
    • ulcer, foreign body penetration, ingrown nail

• Must rule out septic arthritis with aspiration
• If bone is exposed \(\rightarrow\) osteomyelitis
### Labs

- ESR
- CRP
- WBC: left shift
Imaging

- X-rays:
  - Gas
    - Often just normal pathogens
  - Osteolysis
- MRI
  - Good for occult abscess
  - Very poor at distinguishing infection from Charcot
    - Especially in the early stages of either
  - Dx'ing osteomyelitis:
    - bone marrow changes + soft tissue findings

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Imaging

- Bone scan: Technetium-99m $^{99m}$ Tc
  - Three phase not specific
  - Helpful if negative
  - Non-specific
    - Bone changes can be seen at one year
Bone biopsy

• Definitive test for osteomyelitis
• Deep abscess culture at same time

Treatment

• Aggressive debridement
• Relieve pressure in abscess and remove dead tissue
  – Resect metatarsal heads, bony prominences
Antibiotics

• IV Vancomycin and Zosyn until final cultures
• Adjust for renal function
• Tetanus

• Consult Infectious Disease!

Amputations
Amputation, A Historical Perspective

• Anthropological evidence credits the earliest amputations to cave paintings uncovered in Spain and France nearly 36,000 years ago.
  – practice of self-mutilation to appease gods during religious ceremonies
• Oldest recorded surgical procedure
• Documented in the Rig-Veda (c. 1200 BC) and the Temple of Ramses II (13th century BC)

Amputations

• > 50% of all major amputations are in DM
• 50% will lose the contra lateral limb within 3 years

• > 50,000 major limb amputations per year in the United States
• 85% are below-knee amputations
Amputations

• 14 to 24% of patients with an ulcer will require a major amputation
• Lifetime risk for developing an ulcer: 25%
  – Once a patient has an ulcer – 8x chance of an amputation

Deadly

• After amputation there is a 36% mortality rate in 1 year
• 66% of diabetics with an amputation will die within 5 years
Not all that bad…

• Can be a positive procedure
  – 1st step on the road to restored or renewed function
• Beginning of rehabilitation for these patients

Goals

• Salvage as much of the functioning foot as possible
• Partial foot amputations are worthwhile:
  – allow the use of fairly normal shoes with minor modifications
  – Greater mobility
  – Superior function
  – Lower energy consumption
  – Better weight bearing surface
  – Better cosmesis
Charcot arthropathy

Charcot Arthropathy

- Disease of bones and joints in patients with sensory neuropathy:
  - Progressive
  - Destructive
  - Non-infectious
Potential Causes

- Diabetes Mellitus**
- Tabes Dorsalis
- Poliomyelitis
- Tertiary Syphilis
- Leprosy (Hansens dz)
- Syringomyelia
- Pernicious anemia
- Multiple sclerosis
- Paraplegia
- Riley-Day syndrome
- Peripheral nerve lesions
- Spinal cord lesions
- Intra-articular injection of corticosteroids

Epidemiology

- 0.1-5% of patients with peripheral neuropathy will eventually develop Charcot arthropathy
- 50-60 years of age
- Simultaneous involvement rare
Diabetes and Charcot

- Incidence 3-5%→ 13%
- Type 1:
  - Presents after 20-24 yrs after diagnosis
  - 5th decade
- Type 2:
  - Presents after 5-9 yrs
  - 6th decade
- Bilateral in 30 %
- Present radiographically: 1.4%
- Increasing rates:
  - ?increase in incidence or increased awareness

Pathogenesis

- Neurovascular Theory
  - Damage to trophic nerve centers with the alteration in the sympathetic control of blood flow to bones and joints leads to persistent hyperemia and active bone resorption.
- Neurotraumatic Theory
  - An extreme progression of degenerative joint disease following loss of proprioception and protective pain sensation
- PROBABLY BOTH! + Tumor Necrosis factor-a and IL-1
A Unified Theory

Clinical Diagnosis
Acute Charcot

- May occur rapidly or over a few months
- Warm, inflamed and swollen
  - may follow trauma, typically a 5 week delay
  - 3.3°C warmer
- Commonly misdiagnosed as cellulitis, osteomyelitis or inflammatory arthropathy as gouty or septic.
- Pain (>50%), discomfort.
- Diagnosis by exclusion as lab values in early stages are negative.

Investigations

X-ray: Early; absent or subtle finding.  
Late; bone and joint destruction, fragmentation.

- How to distinguish from OM???
  - Three-phase technetium Tc-99m methylene diphosphonate scintigraphy, followed by indium In-111–labeled leukocyte scintigraphy,
  - Sensitivity: 93% to 100%
  - Specificity: ~80%.
- Systemic symptoms and laboratory findings are typically absent in a Charcot fracture
Chronic Charcot

- May be months, painless, without temperature difference or deformity
- Reactivation by further trauma is frequent.
- Patients are at high risk of ulceration and amputation

- High index of suspicion is necessary so that appropriate treatment is immediately instituted to prevent severe deformity!
Stage 0: Inflammation

- Characterized by:
  - Erythema
  - edema
  - rubor
- No structural changes
- Normal X-rays
- Mimics deep infection or cellulitis
MRI

- Can show earliest signs
- 4 to 6 weeks after presentation shows areas of significant bone marrow edema of the navicular, medial, middle, and lateral cuneiform bones, and at the bases of several metatarsal bones.

Offers the highest diagnostic accuracy: ligamentous disruption, concomitant joint deformity, and the center of signal enhancement within joints and subchondral bone (In complex regional pain syndrome no changes occur)

Stage 1: Fragmentation

- Plain radiographs:
  - Bone resorption
  - Periarticular fragmentation
  - Joint dislocation
- Foot is warm and edematous
- Increased ligamentous laxity
Stage 2: Coalescence

- Radiographs:
  - bony consolidation
  - osteosclerosis
  - absorption of small bone fragments
  - fusion of joints
  - sclerosis of the bone
- Edema and warmth decrease

Stage 3: Reconstruction

- Osteogenesis
- Decreased osteosclerosis
- Progressive fusion
- Radiographs:
  - Decreased sclerosis and bony remodeling signify that the deformity (for example, subluxation, incongruity, and dislocation) is permanent
Joints Affected

- Tarsometatarsal joints - 60%
- Metatarsophalangeal joints – 30%
- Tarsal articulations – 24% (Chopart’s > subtalar)
- Ankle – 11%
- Interphalangeal joint – 5%

Brodsky’s anatomic classification
Staging (Brodsky)

• Type I
  – Involve tarsometatarsal and naviculocuneiform joints.
  – Bony prominences
  – Predispose to soft tissue breakdown and ulcerations
  – Most common clinical presentation

Staging

• Type II: ST or Chopart joints
  – Persistent instability
  – Unlikely to produce bony prominences or ulcerations

• Type IIIa: Ankle
  – Longest period of persistent instability (varus/valgus collapse)
  – Require long term immobilization
  – Produce bony prominences, less often than Type I

• Type IIIb: Calcaneal tuberosity
Staging

- Type IIIb
  - Develop neuropathic fracture of the posterior tubercle of the calcaneus.
  - Leads to secondary acquired pes planus.
  - Treatment is either total contact cast followed by accommodative footwear.

Treatment

1. Immobilization
2. Pharmacological Treatment.
3. Surgical Treatment.
Treatment

- Cessation of weight-bearing
- Cast immobilization should be applied until edema has subsided and the condition has stabilized.
  - Care must be taken to protect the neuropathic foot beneath the cast. (pressure points)
- Immobilization is maintained for a minimum of 8-12 weeks.
- Removable casts used for the transition from non-WB to full WB
- Long term CMO of CROW are used long term

Treatment (Immobilization)

- Strict immobilization of the foot and ankle in an attempt to stabilize and protect the foot.
- Total contact cast, Unna boot, Jones dressing, or elastic wrap will provide stabilization with non weight-bearing.
- Not supported by randomized control trials
Treatment

• Cast changes every 1-2 weeks with foot inspection and cutaneous temperature (for 3-6 months)
• Serial radiographs every month during acute phase

Treatment (Weight-bearing)

• ?total contact cast which allows some measure of ambulation for the patient
• Decision should be based on clinical judgment
Biphosphonates

• Central antinociceptive effect of calcium.
• Ca influx releases various substances (substance P, vasoactive intestinal peptide, neuropeptide Y, PG, serotonin, and kinines) that are involved in nociception and inflammation
  – Potent inhibitors of osteoclastic resorption

Treatment (oral) \textit{Pitocco, 2005}

• 70 mg of alendronate weekly for 6 months
• All wore TCC for two months then transferred to a pneumatic walker for remaining four months
• Measured type I collagen, hydroxprolin, osteocalcin, testosterone, estradiol, thyroid hormones, PTH, FSH, LH during the six months
• \textbf{Resulted in significant reduction of type I collagen, hydroxyprolin (indicators for bone reabsorption)}
Treatment (oral)

• Anderson 2004
  – 13 pts retrospective study
  – Treated with single infusion of pamidronate and TCC versus TCC
  – Tested for temperature and alkaline phosphatase levels
  – Temp. dropped 2.8 degrees in 48 hours and 7.4 degrees in 2 weeks compared to a 2.3 degree drop in control
  – Alk phos decreased by 53% after 2 weeks compared to 9% in control group

When the cast comes off...

• Reactivation can reoccur!
• Use of some sort of brace to protect the foot (ex. Patella tendon bearing brace)
  – May be eliminated after 6-24 months
  – Then continue with custom footwear to support foot.
Devices

• CAM boot
• PTB (patellar tendon-bearing): can be used with custom molded foot wear. Use of PTB can be tapered after 6-24 months of use, if foot is plantigrade. PTB will decrease vertical force by 15%, this can be increased to 32% by adding padding (Trepman, 2005)
• CROW: full foot rigid walker and custom insole. Similar to a TCC, but removable. Can control edema and allows for ambulation.
• Extra-depth shoes: usually include a rigid shank and a rocker bottom.

Modified/custom shoes/orthoses
Custom Footwear

- Oxford style custom molded shoe.
- Plastazote healing shoe available over the counter.

Continue to Monitor

- Regular examinations.
- Foot ulcerations, subsequent infection and ultimately amputation are common occurrences when a patient with Charcot foot has been improperly managed.
- In a series by Pinzur, over 50% of the patients presenting with neuroarthropathic deformity of the foot had open foot ulcers.
Reconstructive Surgery

- Reserved for patients who have recurrent ulceration despite compliance with the previously mentioned regimens.
- Surgical intervention in diabetic neuropathy has been shunned in the past, however as long as there is adequate vascular supply to the foot, soft tissue healing is possible.

Take Home Points

- Charcot may mimic cellulitis and DVT
- May or may not have associated pain
- Normal radiographs does not exclude
- Treat aggressively:
  - strict immobilization
  - proactive measures
  - Vigilance