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Complications of diabetes: beyond the heart, kidneys, and eyes

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Abstract: Diabetes is a leading global health problem. Clinicians and most patients are aware that diabetes can lead to complications in the heart, kidneys, and eyes. Given the high morbidity and mortality, much effort is made to screen for and treat these complications. Other organ systems can also be affected by diabetes. The pathogenesis and risk factors for developing these other complications does not always match those for heart, kidneys, and eyes. Additionally, treatment for these other complications is often limited or absent. Here we will review some of the major musculoskeletal, neuropathic, and skin complications linked to diabetes. ■ *Heart Metab*. 2019;80:23-27

Keywords: autonomic; complication; diabetes; musculoskeletal; neurologic; skin

Overview

Diabetes is a growing worldwide health problem. The disease leads to complications across multiple organ systems. Clinicians taking care of patients with diabetes worry most about increased risk for cardiovascular disease, renal failure, and vision loss. Reducing these risks involves reducing blood sugar levels and controlling blood pressure, as well as lipid-lowering therapy. This treatment strategy highlights the role of metabolic dysregulation and/or inflammation in pathogenesis of these diabetes complications.

Many other organ systems can be affected by diabetes. In this review we will summarize some of the major musculoskeletal, neuropathic, and skin complications linked to diabetes *(Table I, Figure 1).* The pathogenesis for these other complications is less understood but likely includes factors such as fibrosis, hypercoagulability, and ischemia in addition to metabolic dysregulation. Treatment of these complications is often either absent or less effective.

Musculoskeletal complications

Fibrosis is a prominent feature of the musculoskeletal complications of diabetes.[1-4] The fibrosing conditions are characterized by increased swelling, inflammation, and reduced mobility of the involved joints. Fibrosis is thought to begin with glycosylation of connective tissue components leading to activation of fibroblasts and inflammatory mediators. Fibrosis is most noted in the shoulder and hands:

- Frozen shoulder, also known as adhesive capsulitis, presents with pain and limited mobility of the joint and often affecting both shoulders
- Limited joint mobility, also known as cheiroarthropathy (cherio = hands in Greek), usually involves the hands. The tissue over the dorsum of the hands develops a waxy and/or stiff appearance. Joint mobility is decreased, especially flexion of the metacarpal-phalangeal (MCP) and proximal interphalangeal (PIP) joints. The disease is usually painless
- Dupuytren's contracture appears with increased frequency in patients with diabetes. The condition is associated with other chronic diseases, and smok-

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ing is a risk factor. There is fibrosis of the palmar aponeurosis that leads to flexion contractures of one or several digits.

- Trigger finger involves fibrosis and/or inflammation of a finger's flexor tendon and its sheath. This leads to "locking" of the involved finger in a flexed position.

Other musculoskeletal manifestations of diabetes are more related to inflammation, microvascular changes, and alterations in nerve function. These processes affect the spine, legs, and feet:

- Neuropathic arthropathy, also known as Charcot's joint, affects the bones of the ankles and feet. Changes in nerve function alter the biomechanics of walking, leading to bone microfractures. Altered autonomic activity disturbs blood flow and contributes to increased bone resorption. The initial phase of the disease is characterized by warmth, swelling, and erythema of the foot. Progressive destruction of the joints occurs with collapse of the arch, leading to the rocker-bottom deformity
- Diffuse idiopathic skeletal hyperostosis (DISH) involves calcification of tendons and ligaments. The disease primarily affects the thoracic and lumbar spine. Patients report stiffness, reduced range of motion, and sometimes pain. Diagnosis is made by x-ray imaging
- Muscle infarction is a rare condition which presents with pain and swelling of a muscle group, typically thigh or calf. The disease is relatively rare and specific for diabetes. Vascular changes, hypercoagulability, and inflammation are all thought to be contributing factors.

Neuropathic complications

Neuropathy is present in up to half of all patients with diabetes. Prevalence increases with increasing duration of diabetes.[5] The pathogenesis is poorly understood. Microvascular dysfunction, altered neuronal metabolism, and direct toxic effects of glucose have all been proposed as mediators of damage. The disease is notable for attacking primarily sensory neurons. The neuropathy syndromes are classified as distal symmetric polyneuropathy, various focal neuropathies, and autonomic neuropathy.

Symmetric polyneuropathy is the most common type of diabetic neuropathy. It is characterized by loss of sensation in the distal extremities (glove and stocking distribution). About 50% of patients report pain sensation described as "burning." Diagnosis is made based on clinical exam findings which include loss of pinprick, temperature, vibration, and proprioception. Diminished ankle reflexes frequently accompany distal neuropathy. Treatment is not very effective and is based on use of anticonvulsants (ie, pregabalin, valproate), antidepressants (amitriptyline), and opioids.[6]

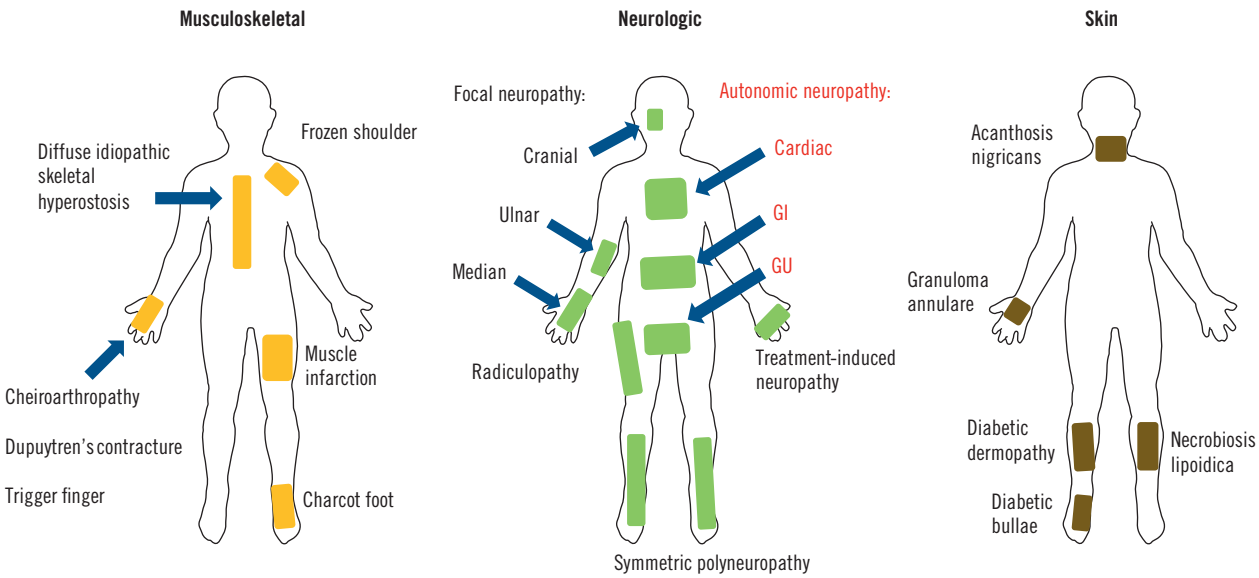

Figure 1 *Complications of diabetes.The figure highlights some of the organ systems and anatomic locations affected by diabetes. Left, musculoskeletal complications associated with diabetes. Middle, neurologic complications. Right, skin complications.*
Adapted from ref 5: Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. Nat Rev Dis Primers. *2019;5:41.*

Focal neuropathy (polyradiculopathy, mononeuropathy, mononeuropathy multiplex) involves one or several nerves/nerve roots and thus presents with isolated symptoms.

Polyradiculopathy refers to disease caused by damage to nerve roots, particularly in the cervical, thoracic, and lumbar spine. Onset is usually rapid with pain a prominent early component, followed by proximal weakness. Presentation is often unilateral but eventually bilateral involvement is common. Symptoms often resolve over time. Immunotherapy has been proposed as treatment of diabetic polyradiculopathy[7]:

- Cervical polyradiculopathy typically starts acutely with pain, weakness, and loss of sensation in the upper extremities.[8]
- Thoracic polyradiculopathy presents with abdominal pain and weight loss.[9] Findings on exam include abdominal wall paresis and/or paresthesias. Diagnosis can be challenging as many disorders can lead to abdominal pain
- Lumbar polyradiculopathy is characterized by pain and proximal limb weakness as well as weight loss.[10]

Focal mononeuropathy is a disease of an individual peripheral nerve. In the focal mononeuropathies direct mechanical trauma (ie, entrapment) can be a contributing factor above and beyond those listed above. The chance for recovery is best with milder cases. Median nerve neuropathy (carpal tunnel syndrome) is the most common focal mononeuropathy in diabetes but also occurs frequently in the general population.[1]

Musculoskeletal		
Complication	*Location*	*Manifestation*
Frozen shoulder	Shoulder	Pain, stiffness, reduced mobility
Cheiroarthropathy	Hands	Waxy skin, stiff joints
Dupuytren's contracture	Finger	Flexion contracture
Trigger finger	Finger	Locked in flexion
Carpal tunnel syndrome	Hand	Pain and paresthesias
Charcot foot	Foot	Inflammation, collapse of foot arch
Diffuse idiopathic skeletal hyperostosis	Spine	Stiffness, reduced range of motion
Muscle infarction	Thigh	Pain and swelling
Nerve		
Complication	*Location*	*Manifestation*
Symmetric polyneuropathy	Distal extremities "glove and stocking"	Decreased sensation, burning pain
Radiculopathy	Cervical, thoracic, and/or lumbar spine	Pain+weakness of affected region and weight loss
Mononeuropathy	Isolated nerve involvement	Decreased sensation/function of affected nerve
Cardiovascular autonomic neuropathy	Cardiovascular system	Tachycardia, orthostatic hypotension, exercise intolerance, silent ischemia
Gastrointestinal autonomic neuropathy	GI tract	Reflux, gastroparesis, diarrhea
Genitourinary autonomic neuropathy	GU system	Overflow incontinence, dyspareunia, erectile dysfunction
Peripheral autonomic neuropathy	Feet	Edema and dry skin with increased sweating in the proximal limb
Treatment-induced neuropathy	Distal extremities (+/- autonomic neuropathy; +/- retinopathy/nephropathy)	Burning pain
Skin		
Complication	*Location*	*Manifestation*
Diabetic dermopathy	Shins	Small, well-demarcated, hyperpigmented, and depressed lesions
Necrobiosis lipoidica	Anterior shin	Yellowish, atrophic plaques with purplish borders
Granuloma annulare	Dorsum of hands and feet	Grouped papules that expand in an annular shape
Acanthosis nigricans	Folds of the neck	Hyperpigmented, hyperkeratoic areas
Diabetic bullae	Feet	Spontaneous blisters

Table I *Summary of musculoskeletal, neuropathic and skin complications in diabetes.*

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The pathophysiology centers around entrapment of the median nerve, although in diabetes there may be intrinsic damage to the nerve itself. Symptoms include tingling, pain, and paresthesias of the thumb, index, and middle fingers which can be elicited in the clinic by employing Tinel's test (percussion of the median nerve) and Phalen's test (dorsiflexion of the wrists). Other sites involved in diabetic focal mononeuropathy include the ulnar, peroneal, and cranial nerves. Mononeuropathy multiplex is similar to focal mononeuropathy but involves multiple individual nerves.

Autonomic neuropathy is common and likely underdiagnosed in diabetes patients.[11] Incidence increases with duration of disease and worsening glycemic control. Treatment is focused on reducing blood glucose levels. Autonomic neuropathy can affect the cardiovascular system, gastrointestinal tract, genitourinary system, and peripheral tissue:

- Cardiovascular autonomic neuropathy usually presents with resting tachycardia. This can be associated with decreased heart rate variability. Progression of cardiovascular autonomic neuropathy can lead to a fixed heart rate, exercise intolerance, orthostatic hypotension, and silent ischemia[12]
- Gastrointestinal autonomic neuropathy causes both upper GI symptoms (ie, reflux and gastroparesis) and lower GI symptoms (diarrhea).[13,14] Symptoms of gastroparesis include nausea, early satiety, vomiting, and abdominal pain. Diagnosis can be made by measuring gastric emptying. Patients with diabetes can also develop dumping syndrome, or rapid gastric emptying. Diarrhea related to autonomic neuropathy is watery, may alternate with bouts of constipation, and can be associated with fecal incontinence
- Genitourinary autonomic neuropathy can cause overflow incontinence of the bladder, dyspareunia in women, and erectile dysfunction as well as retrograde ejaculation in men
- Peripheral autonomic neuropathy leads to impaired autonomic control of sweat glands and blood flow distally. Patients notice dry, itchy, and swollen feet with increased sweat production more proximally.[5] The changes in skin and blood flow likely contribute to the development of diabetic foot ulcers.

Treatment-induced neuropathy is a rare category of diabetic neuropathy which occurs in patients with poor glycemic control who experience a rapid improvement in blood sugar levels.[15] Type 1 diabetes and prolonged hyperglycemia are risk factors for this complication. Studies suggest that a greater than 3% decline in HbA_{1c} over a period of 3 months or less greatly increases the risk of developing treatment-induced neuropathy. Although the syndrome was previously known as "insulin neuritis," any treatment modality that acutely lowers blood glucose can trigger the disease. Patients note rapid onset of "burning" neuropathic pain in the distal extremities. This can be accompanied by autonomic neuropathy. The severity of involvement increases with the magnitude of blood-sugar lowering. Treatment-induced neuropathy is managed by slowing the decline in A_{1c} levels. Interestingly, patients who have treatment-induced neuropathy are also at risk for acutely developing worsening retinopathy and nephropathy, suggesting a common underlying microvascular cause for all three conditions.

Skin complications

Most clinicians are familiar with the cellulitis which can appear in a poorly perfused insensate foot of a patient with diabetes. However, there are many other skin lesions which can be found in patients with diabetes.[16] These skin lesions are sometimes the first indication of the presence of systemic disease. Diabetes-related skin findings are more common in patients with poor glycemic control. The pathogenesis is poorly understood but direct glucose toxicity, fibrosis, and altered immune function are all thought to play a part:

- Diabetic dermopathy is common in patients with diabetes.[17] The characteristic findings are small, well-demarcated, hyperpigmented, and depressed lesions, usually on the shins
- Necrobiosis lipoidica is a relatively rare granulomatous disease of the skin associated with diabetes.[18] It manifests as yellowish plaques affecting the anterior shin. The plaques have purplish borders with central atrophic-appearing skin
- Granuloma annulare occurs in diabetes as well as other medical conditions. It appears as grouped papules that expand in an annular shape, typically in the dorsum of the hands and feet
- Acanthosis nigricans occurs as hyperpigmented, hyperkeratotic areas, typically in the folds of the skin which is associated with insulin resistance/diabetes. It is often an early visible manifestation of insulin resistance

- Diabetic bullae are recurrent spontaneous blisters that appear mostly in the feet of patients with diabetes.[19]

Conclusion

Clinicians devote a lot of energy to monitoring and managing the cardiovascular, renal, and eye complications of diabetes. It is important to consider that the disease affects other organ systems. In this review we have summarized some of the major musculoskeletal, neuropathic, and skin complications linked to diabetes. The pathogenesis of these complications involves not only metabolic dysregulation and inflammation but also fibrosis, hypercoagulability, and ischemia. Unfortunately, there are generally few treatment options for these complications, and even simple relief of symptoms can be challenging. Perhaps in future better prevention and/or control of diabetes will reduce the frequency and severity of these complications. ■

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