

Pathophysiology of Diabetes and Charcot Neuroarthropathy

2

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Introduction

This chapter serves as a primer on the pathophysiology of both diabetes mellitus and Charcot arthropathy for the orthopedic surgeon. In regards to diabetes we will focus on the pathophysiology as it pertains to musculoskeletal manifestations of the disease process. The pathophysiology that underlies the development of diabetes is beyond the scope of this chapter. We will discuss both the historic theories of pathogenesis and identify modern theories and advancements in the understanding of Charcot arthropathy, a progressive disease that leads to degeneration of joints, especially to those of the foot and ankle.

Diabetes Mellitus

Diabetes mellitus is a disease of glucose metabolism. It has many different underlying etiologies, which have become increasingly important to understand as its prevalence has increased tre-

mendously in both the United States and globally. It has been reported that over 29 million people have diabetes in the United States alone [1]. The many complications associated with diabetes can affect multiple end organ systems. The disease is one of the leading causes of death, blindness, renal failure, and amputation [1] and the cost associated with treating the disease and its associated complications surpassed \$245 billion in 2012 [2].

There are two predominate types of diabetes: Type I, historically known as insulin-dependent diabetes, and Type II, formerly known as non-insulin-dependent diabetes. The fundamental difference between the two types is the way in which glucose metabolism is altered. In type I diabetes, insulin production is limited within the pancreas by an autoimmune process. In type II diabetes, insulin receptors are downregulated throughout the body resulting in insulin resistance. In either case, the result is deranged blood glucose control and periods of hyperglycemia. One focus of this chapter is to explore the pathogenesis of musculoskeletal complications in diabetes as it applies to both types I and II.

Charcot Arthropathy

Charcot arthropathy is a progressive and destructive disease process that affects the joints of the extremities in patients with neuropathic

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conditions [3]. Today it is most commonly associated with diabetes and is often found in the foot and ankle [3, 4]. Charcot arthropathy has historically been known as a rare disease; however, with increasing rates of obesity and increasing prevalence of diabetes, the impact of this devastating disease process, on both patients and healthcare dollars, will continue to increase [1, 2]. It is estimated that up to one in three patients with diabetic neuropathy will develop an arthropathy [5].

Charcot arthropathy was first described in the late 1868 by the neurologist Jean-Martin Charcot in patients with *tabes dorsalis* [6–8]. He described an acute onset of pain followed by joint destruction ultimately leading to impaired function. At that time, “Charcot’s joint” was most commonly associated with syphilis and it was not until 1936 that the association to diabetes was made [7–9].

The disease process is often initiated by subtle or insignificant trauma to the joint of a neuropathic patient. The clinical and radiographic progression has been classically described by Eichenholtz as occurring in three distinct stages (see Fig. 2.1) [10]. Stage I (acute or developmental phase) is identified with swelling, erythema, warmth of the extremity and bony fragmentation on radiographs. This phase is often confused with a soft tissue infection, abscess or cellulitis, especially in the diabetic patient, leading to a delay in treatment. An important finding on physical exam is the resolution or improvement in erythema with elevation of the extremity [11] (See Table in the Appendix). The presence of dependent erythema is usually associated with Charcot arthropathy. It should also be noted that infection without the presence of a wound or ulcer is rare and that a diagnosis of a Charcot arthropathy should be strongly considered [11, 12]. Eichenholtz Stage II (coalescent or quiescent phase) is marked by improvement in swelling and erythema and consolidation of fracture fragmentation on radiographs. Stage III (reconstruction phase) is highlighted by ankylosis of joints and hypertrophy of the bone. Through the progression of the arthropathy, the patient may develop a deformity, instability, and dysfunction of the involved joint. Infection not only plays a role in confounding the diagnosis of Charcot

arthropathy, it is also a late complication. That is because the development of hypertrophic exostoses may cause an, altered gait and instability, and may lead to the development of an ulcer. These ulcers are challenging to manage due to both micro- and macro-vascular disease, along with an impaired immune function. This constellation of complications: deformity, dysfunction, and infection, creates significant problems for the orthopedic surgeon and unfortunately may be limb threatening.

Pathophysiology of Diabetes

The pathophysiology surrounding the complications of diabetes, as it pertains to the musculoskeletal system, will be reviewed. Intuitively and academically proven, diabetic patients are at higher risk for surgical site infections, foot ulcers, and poor bone healing. The underlying reasons can be explained in part by an impairment of the vascular system, nervous system, and immune system. These are summarized in Table 2.1.

Vascular System

Diabetes can lead to both microvascular and macrovascular disease through a dysfunction of endothelial cells and vascular smooth muscle [13]. Periods of hyperglycemia are a trigger for cellular dysfunction and dysregulation, by altering the normal coagulation pathways. This leaves vessels predisposed to thrombosis. The end product is reduced blood flow at the tissue level. This limits healing by allowing waste product accumulation and a lack of nutrient delivery. In the setting of infection, this vascular dysfunction will cause the delivery of antibiotic therapies to be limited. Please see Chap. 3 for further discussion of the vascular problems associated with diabetes.

Endothelial Cell Dysfunction

The endothelial cells, which line the vessels throughout the vascular system, play a crucial role in balancing blood flow. This is done on a local

Fig. 2.1 AP and lateral foot radiographs depicting the three Eichenholtz stages of Charcot neuroarthropathy. **(a)** Stage I—*acute phase*, note the prominent soft tissue swelling and early bony fragmentation, **(b)** Stage II—*coalescence phase*, improved swelling, beginning of callus formation, **(c)** Stage III—*reconstructive phase*, ankylosis of the midfoot and first tarsometatarsal joints



level through paracrine factors. High glucose levels decrease the levels of nitric oxide (NO), a locally active vasodilator [14]. The excess glucose is taken into the endothelial cell where protein kinase C (PKC) is activated in the mitochondria. The PKC activation is then accompanied

by the production of radical oxygen species (ROS). It is through this mechanism that the majority of hyperglycemia-induced ROS are produced. Superoxide ions, a specific ROS, reduce the NO to peroxynitrite. Peroxynitrite easily passes through the membrane of endothelial cells

Table 2.1 Mechanisms of pathophysiology in diabetes mellitus by system

Vascular system	Endothelial cell dysfunction	NO imbalance, production of ROS
	Vascular smooth muscle dysfunction	PKC activation, ROS production, Monocyte activation, proinflammatory state, fibrosis
	Coagulation and platelet dysfunction	NF- κ B activation \rightarrow proinflammatory state, increased TF activation and increased PAI-1 Levels \rightarrow thrombosis
Nervous system	Oxidative stress	Production of ROS, decreased synaptic NO, formation of AGEs, activation of RAGE, activation of NF- κ B \rightarrow proinflammatory state, mesenchymal stem cell apoptosis
	Microvascular disease	Neural hypoxemia, intraneural vascular hyalinization, thrombosis, loss of regulation of neural bloodflow
Immune system	Innate immune system dysfunction	Decreased complement, increased basal levels of TNF- α , IL-6, IL-8 via NF- κ B activation, decreased inflammatory response from PBMCs in setting of stimulation, impaired PMN chemotaxis
	Adaptive immune system dysfunction	Monocyte/Macrophage dysfunction, IgG inactivation by glycosylation

NO nitric oxide, ROS reactive oxygen species, NF- κ B Nuclear Factor Kappa-light-chain-enhancer of active B cells, TF tissue factor, PAI-1 plasminogen activator inhibitor-1, AGEs advanced glycation end products, RAGE receptor for advanced glycation end products, TNF- α tumor necrosis factor alpha, IL interleukin, PBMCs peripheral blood mononuclear cells, PMN polymorphonuclear cells, IgG immunoglobulin G

and causes nitrosylation of the enzymes involved in the synthesis of NO. Through this mechanism, hyperglycemia leads to both reduction and impaired synthesis of NO, via the generation of ROS. The inability to regulate NO results in vasoconstriction [13, 14].

Vascular Smooth Muscle Dysfunction

The PKC activation also causes structural changes in the vascular architecture, induces the production of vascular inflammation, and causes the ROS to increase the transcription of proinflammatory genes. These genes include monocyte chemoattractant protein-1, vascular cell adhesion molecule-1, and intracellular adhesion molecule-1. When activated, these genes result in the adhesion of circulating monocytes to the endothelium. These activated monocytes then secrete inflammatory mediators, such as interleukin (IL)-1 and tumor necrosis factor alpha (TNF- α). The subsequent inflammatory state leads to fibrosis and dysfunction of the vascular smooth muscle, leading to narrowing of vessel caliber [15, 16].

Coagulation Dysfunction

In normal conditions, insulin inhibits platelet aggregation through tissue factor (TF) inhibition and decreased plasminogen activator inhibitor-1 (PAI-1) levels [17]. However, in type II diabetes,

insulin resistance is associated with increased cellular PAI-1 levels, thereby reducing tissue plasminogen activator levels, a known thrombolytic agent. This results in diabetic patients, especially those with type II diabetes, to become prothrombotic

There are multiple theories explaining the dysfunctional coagulation seen in the diabetic patient [13, 17–19]. Free fatty acid (FFA) levels are increased in most patients with type II diabetes. These FFAs bind to toll-like receptors, which are involved in activating the nuclear factor kappa-light-chain-enhancer of the active B cells (NF- κ B) pathway. The NF- κ B pathway is a proinflammatory pathway. This chronic low-grade inflammatory pathway induces the production of TF and causes an early trigger in the coagulation cascade. The proinflammatory state also causes endothelial cell dysfunction, as described above, which leads to endothelial cell damage. Once the damaged collagen is exposed to circulating platelets and coagulation factors, it leads to thrombosis. This is currently the best theory for this dysfunction.

Nervous System

Neuropathy is a common complication of diabetes. More than 60 % of diabetics have some signs and symptoms of neuropathy [5, 20]. These include

loss of protective sensation, autonomic dysfunction, pain, and weakness. Diabetic neuropathy, coupled with the other complications of diabetes, sets patients up for ulceration, wound breakdown, and poor healing. The mechanisms by which diabetes and hyperglycemia lead to damage of the peripheral nervous system are explained in part by oxidative stress, inflammation, and microvascular disease. It is likely that a complex interaction between these mechanisms and multiple pathogenic processes ultimately leads to the clinical outcome of diabetic neuropathy.

Oxidative Stress

As noted with vascular dysfunction, hyperglycemia leads to an increased formation of ROS, which has a direct affect on NO production in endothelial cells. In the nervous system NO is a common neurotransmitter and ROS formation causes a reduction of the intracellular production of NO in neurons. This ultimately leads to dysfunction of the nerve.

Hyperglycemia also leads to the formation of advanced glycation end products (AGEs) by reducing reactions of protein amino groups [21, 22]. In addition to producing neurologic abnormalities, AGEs also have profound effects on the vasculature system and are deposited in collagen of soft tissues leading to muscle and tendon dysfunction. This contributes to altered gait patterns and predispose patients with peripheral neuropathies to microtrauma.

During its formation more ROS are liberated. This results in species that bind to the receptor for advanced glycation end products (RAGE), a transmembrane protein. This causes an activation of the NF- κ B pathway. This leads to upregulation of the RAGE receptor, which increases the production of ROS, and leads to an increase in the numbers of proinflammatory mediators. This directs activated RAGE receptors towards apoptosis of mesenchymal stem cells [23]. Activation of this pathway sets the stage for chronic and unchecked inflammation.

Microvascular Neurologic Disease

It is believed that the vascular changes caused by hyperglycemia also lead to decreased endoneurial blood flow and nerve ischemia. Endoneurial

blood flow is controlled through a process of arteriovenous shunting that is regulated by unmyelinated nerve fibers. When these regulatory nerve fibers are damaged there is a loss of regulation of blood flow to the nerve and hypoxemia is exacerbated. This is often associated with a decrease in motor neuron function. The structural changes that occur at the level of the intraneural vasculature include hyalinization and vessel wall thickening, similar to the changes that occur with microvascular disease. These changes include fibrin deposition, platelet activation, and thrombosis formation in the vessels supplying peripheral nerves.

Immune System

It has long been established that there is a degree of immune system dysfunction associated with diabetes. This dysfunction, coupled with that occurring to the vascular and nervous systems, predisposes diabetics to infections that can be difficult to treat and are potentially limb threatening. Diabetes has been associated with many derangements in the innate immune system but there has also been dysfunction noted in the adaptive immune system.

Innate Immune System

Diabetes has been found to affect the function of the innate immune system through multiple mechanisms [24, 25]. The innate immune system is a nonspecific host defense against pathogens. Its main components consist of physical epithelial barriers, phagocytic leukocytes, dendritic cells, a special type of leukocyte known as a natural killer (NK) cell, and circulating plasma proteins. In many cases it is the first line of defense against infection.

The complement system is a complex and integral part of the innate immune system that amplifies the response against a pathogen and ultimately results in cell death. Patients with diabetes have been shown to have a lower than normal serum concentration of complement factor 4 (C4), which is an important part of the complement pathway [26]. However, the clinical relevance of the reduced C4 levels in diabetics remains unclear.

As previously noted, hyperglycemia, and especially diabetes, increase production of ROS, which activates the NF- κ B pathway and increases proinflammatory cytokines, predominately TNF- α , IL-6, and IL-8. These inflammatory cytokines play a critical role in regulation of the immune system in times of infection. However, due to persistent hyperglycemic conditions, the serum levels of these cytokines are chronically elevated [27, 28].

Due to chronically elevated cytokines, the response to an infection is decreased. Polymorphonuclear cells (PMNs) are the phagocytic cells of the innate immune system that predominate in the circulation. In order to gain access to a site of infection they undergo the process of chemotaxis. During this process, the cells migrate towards areas of infection or inflammation, following a chemical gradient of various cytokines. It has long been established that the PMNs of diabetic patients have defective chemotaxis [24]. Interestingly, the levels of inflammatory cytokines, produced from peripheral blood mononuclear cells of diabetic patients, do not increase as expected when stimulated with lipopolysaccharide (LPS), a component of gram-negative bacteria. One theory is that the constitutively active monocytes of diabetic patient may grow tolerant to their stimulated environment and their response is often blunted in the setting of infection.

Adaptive Immune System

The adaptive immune system is responsible for historic immunity against pathogens. It is called into action against pathogens that are able to evade or overcome the innate immune defenses. When activated these components “adapt” to the presence of infection by activating, proliferating, and creating potent mechanisms for neutralizing or eliminating microbes. Diabetes has generally not been associated with derangements in the adaptive immune system; however, there are some observations that have been made that raise the concern of dysfunctional macrophage phagocytosis and antibody inactivation. One study has shown that patients with type I diabetes have a decreased antibody titer response to hepatitis B vaccination and have implicated impaired macrophage phagocytosis as the

mechanism [29]. This theory is supported by the macrophage/monocyte dysfunction that is due to chronically elevated inflammatory mediators.

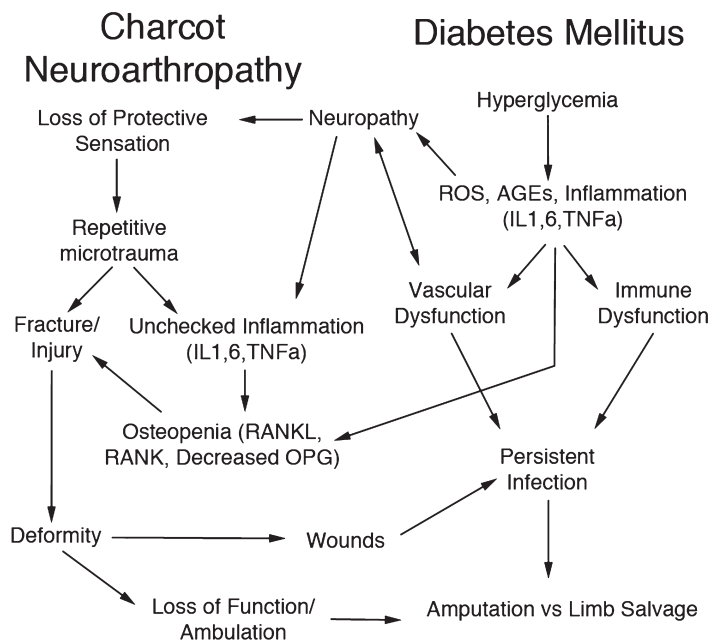
There are two types of adaptive immune responses: humoral immunity, that is mediated by antibodies produced by B lymphocytes, and cell-mediated immunity, mediated by T lymphocytes. Immunoglobulin G (IgG) is a dominant antibody which confers adaptive immunity to individuals who have been exposed to antigens previously. In diabetic patients IgG can become nonenzymatically glycosylated. It is believed that these antibodies do not function as well as normal IgG. Using an animal model, one study examined asplenic rats inoculated with *Streptococcus pneumonia* that were treated with either normal or glycosylated IgG [30]. Those receiving normal IgG lived roughly twice as long than those receiving glycosylated IgG. It appears that glycosylation of IgG leads to inactivation and functional alteration of the adaptive immune system.

Pathophysiology of Charcot Arthropathy

Neurotraumatic and Neurotrophic Theories

Over time, many theories have been developed that have tried to explain the pathophysiology of Charcot arthropathy. Jean-Martin Charcot promoted the *French Theory*, in which it was believed that damage to the spinal cord or nerves resulted from an injury to vasomotor nerves, resulting in loss of the neural control over the vasculature [7, 31]. Volkmann and Virchow described the *neurotraumatic theory*, which described a process where the bones and joints changed due to repeated microtrauma in patients that cannot sense pain [7]. The *neurovascular or neurotrophic theory*, an advancement on Charcot’s French Theory, described an autonomic neuropathy predominated by sympathetic denervation, leading to an increase in arteriovenous shunting and local blood flow by 30–60 %. This was thought to stimulate osteoclast activity and flush away the necessary minerals for bone formation, leading to the development of osteopenia.

Fig. 2.2 Summary figure depicting the major pathophysiologic steps and interactions between diabetes mellitus and Charcot neuroarthropathy. *ROS* reactive oxygen species, *AGEs* advanced glycation end products, *IL* interleukin, *TNF-α* tumor necrosis factor alpha, *RANK* receptor activator of NF-κB, *RANKL* receptor activator of NF-κB ligand, *OPG* Osteoprotegerin



Modern Theory

The pathogenesis of Charcot arthropathy has proven to be complex and continues to be under investigation [31, 32]. However, it is clear that aspects of both the neurotraumatic and neurovascular theories contribute to the disease process. More recently, the role of inflammation, bone turnover, and neuropeptides have become the key topics discussed in the literature [32–35]. Charcot arthropathy has now become closely associated with diabetes, which is likely due to the rise in the prevalence of type II diabetes. Lately, more attention has been spent on the interaction between these two diseases. The degree of overlap between the two disease processes is depicted in Fig. 2.2.

Role of Inflammation and Bone Turnover

In normal physiologic conditions, inflammation is a natural response to injury. One hallmark of a proinflammatory state is pain, which limits the motion and stress an individual places on an injured extremity. However, in the setting of neuropathy, patients lack the ability to sense pain, leading to repetitive trauma to the injured extremity. In Charcot arthropathy, the resulting bone and

joint destruction described in the neurotraumatic model, was once thought to be a directly related to the trauma itself. However, the classic changes that are seen are actually related to an unchecked inflammatory cascade that results from the repetitive microtrauma. A finding that strengthens this theory is that Charcot patients have been shown to have significantly lower bone mineral density than non-Charcot diabetics with peripheral neuropathy [36]. This finding holds true for both the affected and unaffected limb, which supports a theory of inflammation-mediated bone resorption rather than solely trauma-related resorption.

A second item identified, that supports a theory of inflammation, is that the intraoperative tissue obtained from Charcot patients have been found to have positive immunohistological staining for IL-1, IL-6, and TNF-α, three hallmarks of inflammation [33]. Lastly, the theory is bolstered by the findings that proinflammatory cytokines lead to activation of the receptor activator of NF-κB ligand (RANKL). The increase in ROS production and nonenzymatic glycation results in the formation of more AGEs, which also activates RANKL. This triggers many downstream cellular pathways that are implicated in Charcot arthropathy. Activated RANKL interacts and binds with the receptor activator of NF-κB (RANK)

and the receptor for advanced glycation end products (RAGE) This leads to further proinflammatory cytokine release and osteoclast maturation. Stimulation of the NF- κ B, RANK, or RANKL is therefore osteoclastogenic, leading to bone resorption. It is this mechanism that has been implicated in the bony destruction and fragmentation that is seen in Charcot arthropathy, along with many other osteoresorptive conditions [35, 37–39].

In patients with normal physiology, this system is kept in check by osteoprotegerin (OPG). This is a glycoprotein, and a member of the tumor necrosis factor receptor superfamily, that regulates bone resorption by reducing the production of osteoclasts, inhibiting the differentiation of osteoclast precursors, and regulates the resorption of osteoclasts *in vivo* and *in vitro*. It acts as a decoy molecule that binds to RANKL preventing its activation of RANK. Normally OPG is upregulated via the NF- κ B pathway, providing a check on uncontrolled osteoclast maturation. However, the repetitive microtrauma seen in Charcot neuroarthropathy leads to persistent inflammation and ultimately to an increased RANKL/OPG ratio.

Role of Neuropeptides

Neuropeptides are important to the overall health of a nerve, which play a role in bone metabolism. In Charcot patients, the nerves have lost the ability to transport cellular nutrients and neurotransmitters. The mechanism that contributes to bone loss and fragmentation is the loss of modulation of bone turnover by secreted neuropeptides. One such peptide is Calcitonin Gene-Related Peptide (CGRP). This peptide exists in two forms, alpha and beta, and is secreted from small sensory nerve terminals. It is intimately involved in osteoblastic activity and maturation. It binds to the CGRP receptor causing an increase in intracellular calcium in osteoblastic cells and stimulates proliferation and collagen synthesis. It has also been shown to cause the release of IL-10, an anti-inflammatory cytokine [34, 40, 41]. A second neuropeptide affecting bone metabolism is nitrous oxide (NO). This neuropeptide has been shown to induce apoptosis of osteoclast progeni-

tor cells in animal models. With denervation, the delivery of NO is limited and cannot act to check osteoclastic bone resorption Together, these neuropeptides reign unchecked, leading to neurologically induced bone loss.

Summary

The clinical challenges associated with Charcot arthropathy are only compounded in the setting of uncontrolled diabetes. Progress has been made in laying a foundation for understanding the biochemical steps involved in the pathogenesis of diabetes. This includes a focus on problems associated with inflammation, bone resorption mechanisms, and the effect on the loss of certain neuropeptides. In addition, diabetic patients also face vascular and immune complications of diabetes, putting them at a greater risk of dysfunction and limb loss. Diabetic neuropathy also adds to the development of Charcot arthropathy but it appears that the pathophysiology associated with diabetes contributes to the overall process as well.

In order to gain a better understanding of the musculoskeletal manifestations associated with diabetes, one should focus on the derangement of the nervous, vascular, and immune systems. There are commonalities among these diverse systems and recent literature explores the affects of inflammatory pathways and proinflammatory cytokines. Understanding the pathogenesis of these devastating and costly diseases may help identify treatment options to preserve function and prevent limb loss.

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