CHAPTER 1
DIABETES AND INFECTIONS

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels (13). The diagnostic cut point of \( \geq 126 \text{ mg/dl} \) (7.0 mmol/l) for fasting plasma glucose and confirmed the long-standing diagnostic 2-h plasma glucose value of \( \geq 200 \text{ mg/dl} \) (11.1 mmol/l) and A1C of \( \geq 6.5\% \).

The vast majority of cases of diabetes fall into two broad etiopathogenetic categories. In type 1 diabetes, the cause is an absolute deficiency of insulin secretion. Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers. In type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. In the latter category, a degree of hyperglycemia sufficient to cause pathologic and functional changes in various target tissues, but without clinical symptoms, may be present for a long period of time before diabetes is detected.

Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome. Long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial and
cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes.

Population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity contribute to the increasing incidence of diabetes (156). The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The urban population in developing countries is projected to double between 2000 and 2030. The greatest relative increases will occur in the Middle Eastern Crescent, sub-Saharan Africa, and India. The greatest absolute increase in the number of people with diabetes will be in India by 2030. In developing countries, the majority of people with diabetes are in the 45- to 64-year age range. In contrast, the majority of people with diabetes in developed countries are > 64 years of age. Diabetes is the seventh leading cause of death in the U.S., affecting 16.8 million Americans in 2006 (19).

The elevated serum glucose levels associated with diabetes mellitus alter host immune responses, resulting in a well-documented increase in the predisposition to infectious processes. Furthermore, the cumulative effect of age-related immune senescence, superimposed on this enhanced risk of infections, can lead to serious and life-threatening infections in elderly patients with DM. Because infection associated with aging can frequently present in a subtle and atypical manner, prompt recognition of infection and treatment with appropriate empirical broad-spectrum antimicrobial agents, in conjunction with surgical intervention, is often necessary to eradicate such infections. Common sites of serious infection associated with DM include the head and neck, biliary tract, and urinary tract, as well as the skin, soft tissue, and bony structures of the feet in particular (27, 116).

Patients with diabetes had a greater (1.42 times) risk of lower respiratory tract infection among T1DM and 1.32 times for T2DM. The risk for urinary tract infection (UTI) for patients with T1DM and T2DM was times 1.96 and 1.24 than in non-diabetics. *Escherichia coli* and *Klebsiella pneumoniae* were the most frequent microorganisms causing UTI (135). A higher prevalence of asymptomatic bacteriuria (ASB) was observed in diabetics than non-diabetics (47). Bacterial skin and mucous membrane infection was 1.59 times for T1DM and 1.33 times for T2DM, and mycotic
skin and mucous membrane infection 1.34 times for patients with T1DM1 and 1.44 times for T2DM. Risks increased with recurrences of common infections (103).

Despite strict glycemic control, diabetic patients have a 1.7-fold probability of developing an ICU-acquired BSI compared to nondiabetic subjects (98). Sepsis of unknown origin was more common in diabetics, and secondary septic foci and disseminated intravascular coagulation were more frequent in diabetics in a study (135). The short-term effects of the intervention consisted of a multifaceted educational program with an interactive meeting, a leaflet, a Web site, and a consultation with the diabetes care provider on self-reported health-seeking behavior for infections of the urinary tract (UTIs) and lower respiratory tract (LRTIs) in patients with type 2 diabetes influenced positively in reducing infection rate among diabetics (146). Diabetic patients with poor postoperative glycemic control (defined as a mean 48-h postoperative capillary glucose (MCG) >11.0 mmol/L or 200 mg/dL) had 2.5 times higher risk for developing surgical site infection than those with a 48-h MCG < or =11.0 mmol/L (34, 95).

Human cells are accompanied by our personal “microbiome” of 100 trillion microorganisms that live symbiotically inside and on our bodies. International Human Microbiome Project has put their effort to understand the extent to which our microbiomes are unique to each one of us as individuals and common to all of us as a species. It has been observed that these microorganisms have influenced our evolution. They are essential to our digestion, metabolism, and immunity. However, they also serve as the source of our infectivity.

Although bacterial colonization and/or infections are generally acknowledged to negatively impact wound healing, the precise relationship between the microbial community and impaired wound healing remains unclear. Studies have shown that host cutaneous defense responses play a key role in modulating microbial colonization. Correlation between relative abundance of Staphylococcus spp and the expression of cutaneous defense response genes and demonstrated that integrating two types of global data sets lends a better understanding to the dynamic governing host-microbe interactions.
“Sociomicrobiology”- bacterial populations often consist of heterogenous communities rather than genetically identical cells with synchronized gene expression profiles. It is thought that their social interactions might affect the evolution of antivirulence drug resistance during infections. Studies have shown that with gross changes in the bacterial environment, such as the onset of infection, can profoundly perturb the sociomicrobiological structure of the bacterial population, driving a minor subpopulation with a mutant hypervirulent phenotype to thrive, prevail and cause severe disease. Diabetic foot infections are but one of the many complex features of otherwise peaceful coexistence.

Infections with rare organisms or at unusual sites occur more frequently in people with diabetes. If not recognised and treated promptly, morbidity and mortality are high in such cases. Rajbhandari et.al reported cases of necrotising fascitis, malignant otitis externa, Fournier's gangrene and psoas abscess occurring in diabetics that needed intensive treatment with antibiotics, surgical debridement and insulin (117).

Chronic periodontitis is an extremely common infection seen in patients with diabetes. Periodontitis is associated with substantial morbidity in the form of tooth loss, which directly affects nutritional status and the quality of life. In addition, this form of chronic infection often adversely affects glycemic control. Although periodontitis rarely causes death, it can lead to more serious infections such as Ludwig's angina and is a major factor in bacteremia. The relation between diabetes and periodontitis has been well established and is gaining widespread attention (92).

The combination of sensory neuropathy, ischemia and direct adverse effect on host defense mechanisms makes patients with diabetes vulnerable to foot infections. Diabetic neuropathies are reported to affect up to 66% of individuals with type 1 diabetes, most frequently in the form of polyneuropathy (54% of the cohort), the remainder including focal, visceral autonomic, and other atypical varieties (40). A high degree of clinical suspicion and vigilance is necessary for early diagnosis of soft tissue infections and their differentiation from noninfected ulcers. Diagnosis and assessment depend primarily on clinical history and physical examination, although
radiographs, scans and laboratory tests may also provide useful clinical data. The ability to detect bone in the base of an ulcer with a blunt sterile probe may be particularly useful in assisting the recognition of osteomyelitis. Most non-limb-threatening infections are caused by Gram-positive cocci, but more serious infections are often polymicrobial.

Individuals with diabetes have at least a 10-fold greater risk of being hospitalized for soft tissue and bone infections of the foot than the individuals without diabetes (25). In Esposito et al study, the lesions were mainly located at the toes and midfoot (33.6 and 30.2%, respectively); 63 (23.2%) patients had multiple ulcers. Seventy (25.8%) patients also had concomitant osteomyelitis. Three hundred and four pathogens, including Gram-positive and Gram-negative aerobes and anaerobes, were isolated in 219/271 patients (80.8%) by culturing debrided tissue (71.2%) or purulent material (28.8%). Infections were polymicrobial in 33.8% of patients. The most common pathogens were *Staphylococcus aureus* (27.3%) and *Pseudomonas spp.* (20.4%); *Enterobacteriaceae, Enterococci, Streptococci* and anaerobes accounted for 11.5, 7.6, 6.9 and 1.9%, respectively (43). Effective treatment is based on a comprehensive strategy of wound care, avoidance of weight bearing, optimal metabolic control, appropriate antibiotic use and, possibly, surgical intervention (28).

Eneroth et al described about three different groups of deep foot infections among diabetics; osteomyelitis only, deep soft tissue infection only and combined infections (osteomyelitis and deep soft tissue infection). The various types of deep foot infections had different characteristics, treatment and prognosis. Patients with a deep soft tissue infection only or a combined infection had a significantly (p < 0.05) higher; (1) body temperature (2) erythrocyte sedimentation rate and (3) white blood count at diagnosis compared with those who had osteomyelitis only. Patients with a deep soft tissue infection only or a combined infection also had a significantly shorter time to surgery (2 and 4 vs. 10 days), higher mean number of surgical procedures and higher percentage of patients had intravenous antibiotics compared with those who had osteomyelitis only. Amputation before healing was more common in patients with a combined infection compared with those who had osteomyelitis only or a deep soft tissue infection only (42). The findings in his study indicate that deep foot infections
in patients with diabetes is a heterogeneous entity, in which the type of deep foot infection is related to choice of treatment strategy and to outcome.

Necrotizing soft-tissue infections of the foot are an important cause of morbidity and mortality in diabetic patients. When fascia and/or muscle are involved, there are significant risks of major amputation (10). Diabetes has been shown in multiple studies to increase the risk of post-surgical infection, morbidity and mortality in patients undergoing surgery, and also an important cause of increased hospital stay and resource utilization (68, 79, 131). Costs for the management of deep foot infections in in-hospital care, surgery, investigations, antibacterials, visits to the foot-care team, orthopaedic appliances and topical treatment from diagnosis until healing or death was found to be significantly high (137).

In diabetic patients, mycotic infections may increase the risk of developing diabetic foot syndrome. In a first study published using data obtained during a conference attended by patients with long-term diabetes mellitus type 1 (DM1), 78/95 patients (82.1%) showed probable pedal fungal infections (Onychomycosis), of which 84.6% (66/78) were mycologically confirmed by direct microscopy and/or culture (Fig.1.1).

![Figure 1.1](image)

**Figure 1.1.** Discolored, disfigured, brittle nails of the toes and fingers suggestive of Onychomycosis.

The high prevalence of fungal infections detected in DM1 as well as in DM2 diabetics is remarkable, especially considering this highly motivated collective. Therefore, it appears that the feet of diabetics require more diagnostic, therapeutic and preventive
care in terms of mycotic infections and sudomotoric dysfunction than previously thought (41, 94). However, little data are available on the prevalence of fungal infections in deep tissues of the diabetic foot wounds; the role of antifungal agents in wound management, the fungal-bacterial interaction between microorganisms in diabetic foot wounds. Moreover, in most part of the world, the conventional culture techniques which are labor intensive and time consuming are being used to identify fungi from biological specimens.