Immunodeficiency in Diabetic Patients

Ghadeer Sameer Aldoobi, Alaa Omar Alahdal, Jabril Zayed Albalawi, Homodi Alawad Homodi Mohamed, Zahra Hassan Al Hamad and Saad Tais Alhrgan

1King Abdullah Medical City, Saudi Arabia
2National Guard Hospital, Saudi Arabia
3University of Tabuk, Saudi Arabia
4Red Sea University, Saudi Arabia
5Buqaiq General Hospital, Saudi Arabia
6King Salman Hospital, Saudi Arabia

*Corresponding Author: Ghadeer Sameer Aldoobi, King Abdullah Medical City, Saudi Arabia.

Received: August 05, 2020; Published: September 29, 2020

Abstract

Introduction: Patients who have diabetes mellitus (DM) are more susceptible to infections than those without DM. Due to the defects seen in the immunity, the course of the infections and increased prevalence of infections are seen more in this group. Cellular and humoral immunity show disturbances. Diabetic polymorphonuclear cells and diabetic monocytes/macrophages also tend to show decreased functions. Higher glucose environment tends to attract certain microorganisms causing infections that affect multiple organs and organ systems, eventually leading to morbidity and mortality of the patients.

Aim of the Work: The review summarizes the physiopathology, associated mechanisms that make DM patients susceptible to developing infections, and major infections seen with diabetes mellitus.

Methodology: This article is a comprehensive review of PUBMED from the year 1999 to 2017.

Conclusion: Novel treatment options and methods to prevent infectious diseases in diabetic patients can be better understood if proper knowledge about immune dysfunctions during hyperglycemia is known. This can, in turn, improve the outcome of treatment of these infectious diseases.

Keywords: Type 2 Diabetes; Immunity; Immune Dysfunction; Hyperglycemia

Introduction

Deficiency of insulin secretion or action or both causes the clinical syndrome of Diabetes mellitus (DM). It is a metabolic disorder where hyperglycemia is seen as a result of the defect of insulin action [1]. One of the largest developing threats in today's century is considered to be DM [2]. Auto-immune mediated pancreatic beta-cell destruction, which leads to insulin deficiency is the primary cause of Type 1 diabetes. Beta-cell autoantibodies are usually present in this type [3,4]. Type 2 diabetes is seen in a patient with insulin resistance where there is an increased glucotoxicity, lipotoxicity, endoplasmic reticulum-induced stress, and apoptosis which could progressively destroy the beta cells [2,4]. Pathogenesis of type 2 diabetes shows beta-cell autoantibodies, a combination of peripheral insulin resistance and dysfunctional secretion of insulin by pancreatic beta cells [2,5].

Reduced response of T cells, neutrophil function, and disorders of humoral immunity are also seen in diabetes apart from the increased susceptibility to infections. Infections in diabetic patients show a more complicated course and further trigger complications associated with DM, like hypoglycemia and ketoacidosis [2].

**Pathophysiology**

A summarization of the major mechanisms associated with the infections are shown below [2].

![Figure 1: Pathophysiology of infections associated with DM [2].](image)

**Complement**

This system has serum and surface proteins, which causes opsonization and phagocytosis of microorganisms with macrophages and neutrophils, which lyses these microorganisms. It also activates the B-lymphocyte and causes antibody production [2]. The reduction of the CD4 cells could be associated with reductions in cytokine response and polymorphonuclear dysfunction [6].

**Inflammatory cytokines**

The interleukin-1 (IL-1) and IL-6 secreted in response to the lipopolysaccharides stimulation is less due to an intrinsic defect in the cells of DM patients. There is also evidence that an increase in glycation can hinder the production of IL-10 by myeloid cells and that of interferon-gamma (IFN-γ) and tumor necrosis factor (TNF)-α by T cells [7]. Glycation also reduces the expression of class I major histocompatibility complex (MHC) on the myeloid cell's surface, which can impair cellular immunity [8].

**Polymorphonuclear and mononuclear leukocytes**

Hyperglycemia causes decreased mobilization of polymorphonuclear leukocytes, chemotaxis, and phagocytic activity. The antimicrobial function is blocked by the hyperglycemic environment due to the inhibition of glucose-6-phosphate dehydrogenase (G6PD), increased apoptosis of polymorphonuclear leukocytes, and reduced polymorphonuclear leukocyte transmigration via the endothelium [7].

**Antibodies**

The biological function of the antibodies may be harmed by the glycation of immunoglobulin that increases the HbA1c in diabetic patients. However, it was also seen that the antibodies' response after vaccination and to common infections is normal in these patients [7].

Common infections associated with diabetes mellitus

Literature has shown that infectious diseases are seen higher in individuals with diabetes as opposed to individuals without [2, 7].

Respiratory tract infections

Common infections are associated with Streptococcus pneumoniae and influenza virus. Anti pneumococcal and influenza vaccination have been recommended for DM patients by the American Diabetes Association (ADA) and the Centers for Disease Control and Prevention (CDC). The WHO has recommended a single-dose vaccine to reduce the mortality and morbidity against the H1N1 virus. Tuberculosis is also seen higher in diabetic patients, and they are more susceptible to develop multi-resistant tuberculosis, where treatment failures and mortality are more. The treatment for TB can complicate glycemic control as the medicines can increase the metabolism of oral antidiabetic drugs. Depression in the immune response where chemotaxis, phagocytosis, and antigen presentation in response to Mycobacterium tuberculosis infection is impaired in turn affecting the T-cell function and proliferation is seen in DM cases with tuberculosis, which can progress to symptomatic disease [1, 9].

Urinary infections

Lack of adequate glycemic control, duration of DM, diabetic microangiopathy, impaired leukocyte function, recurrent vaginitis, and anatomical and functional abnormalities of the urinary tract can increase the risk of UTI in DM. Asymptomatic bacteriuria in DM can progress to pyelonephritis in certain cases [2].

Acute pyelonephritis has a prevalence of 4 - 5 times more in individuals with DM. Apart from Bilateral renal involvement, the clinical presentation is similar to that in non-diabetic patients [7].

Perinephric and/or renal abscesses, emphysematous pyelonephritis (EP) and renal papillary necrosis are the additional complications that DM patients have a risk for [2, 7].

Skin and soft tissue infections

Folliculitis, furunculosis and subcutaneous abscesses are common skin and soft tissue infections seen in DM individuals. These infections can occur during the course of the disease or could be the first sign of it [7]. Infections on foot are a common chronic complication of DM, which can further lead to amputation, osteomyelitis, or death. the clinical signs appear late due to which delay in diagnosis is seen [2]. Three distinct stages of foot infection are:

- Localized infection (infection in the ulcer bed with or without purulent discharge and surrounding erythema).
- Spreading infection (Apart from the local signs of infection spreading erythema, edema, lymphangitis, and lymphadenitis will be seen).
- Severe infection (Ulcers with extensive soft tissue infection, bluish discoloration suggesting lack of oxygen leading to gangrene) [10].

![Figure 2: Infection in ulcer bed with mild surrounding erythema](image-url)
Necrotizing fasciitis, which is the fast and progressive necrosis of the fascia and subcutaneous tissue and Fournier gangrene - fasciitis that is affecting the male genitalia, are also seen. Invasive external otitis and rhinocerebral mucormycosis are two of the serious head and neck infections seen in diabetic individuals. Periodontitis, a chronic inflammatory disease of the gums are four times more commonly seen in diabetic patients. It destroys the supporting structures of the teeth, which are the periodontal ligament and alveolar bone [11].

**Gastrointestinal and liver infections**

Gastrointestinal motility and sensitivity are important in defense against infections. Oral and esophageal candidiasis caused by *Candida albicans* is commonly seen due to the production of extracellular enzymes such as proteinase and phospholipase. Literature also shows DM individuals who have increased susceptibility to Gastritis caused by Helicobacter pylori and other infections by enteroviruses [2,11].

**Conclusion**

The prevalence of infectious diseases is commonly seen in individuals with DM. Increased virulence to certain pathogens seen in a hyperglycemic environment, polymorphonuclear leukocytes immobilization, decreased interleukin production to respond to an infection, dysmotility seen in the urinary and gastrointestinal tracts, decrease in the chemotactic and phagocytic activity are some of the key pathogenic mechanisms.

Immunodeficiency in Diabetic Patients

Infections like malignant external otitis, rhinocerebral mucormycosis, and gangrenous cholecystitis almost certainly affect only diabetic patients. Some infections can also cause major metabolic complications like hypoglycemia, diabetic ketoacidosis, and coma. Mandatory immunization with anti-pneumococcal and influenza vaccines is recommended because it can help reduce the respiratory infections, the frequency and time of hospitalizations, and the mortality related to respiratory infections.

Bibliography