

## Pathophysiology of infectious diseases in diabetes mellitus patients:

### An overview

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### Abstract

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*Diabetes mellitus (DM) is a clinical syndrome associated with deficiency of insulin secretion or action. It occurs when the pancreas gland no longer produces the insulin needed or it occurs when it is not producing enough insulin and the insulin is not working effectively. The diabetes mellitus patients are much more prone to infections because of hyperglycemic condition. In hyperglycemic condition there are several changes in our body responsible for deleterious effects in immune defense mechanism. It may result due to changes in leukocytes functions, complement system and altered in microvascular responses. It has been found that diabetic patients are susceptible to different infectious diseases, such as Malignant external otitis. Rhino cerebral mucormycotic, Gangrenous cholecystitis, Respiratory infections. Urinary tract infections. Gastrointestinal and liver infections. This review enlightens the pathophysiology and the infectious diseases which being responsible for morbidity of diabetic patients.*

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Keywords: hyperglycemic, polymorphoneutrophils (PMN), complement system

### INTRODUCTION

Diabetes mellitus is a disorder occurs due to metabolic problems and is most frequent globally. The main indication of diabetes mellitus is a hyperglycemia in blood which is due to inappropriate pancreatic insulin secretion or low insulin-directed fostering of glucose by target cells. Diabetes mellitus can be assorted into several types, but the two major types are type 1 and type 2. Type 1 DM or insulin-dependent diabetes mellitus (IDDM) in which body fails to produce insulin, and presently requires the person to inject insulin or wear an insulin pump. Type 2 DM or non-insulin-dependent diabetes mellitus (NIDDM), results from insulin resistance, a condition in which cells fail to use insulin properly, with or without an absolute insulin deficiency.

India is amongst the top most countries followed by China and USA where Diabetes still plagues the society with 32, 26 and 18 million cases respectively[1]. In India, data state that diabetes going to affects every 5<sup>th</sup> individual by 2025(40 million diabetes is expected to be 70 million by 2025) [2]. World scenario as per WHO report, says the prevalence of diabetes cases were increasing, where 1.5 million deaths were estimated in the year 2012 directly from diabetes and it is predicted that it will be the 7<sup>th</sup> leading cause of death in 2030[3]. Thus knowing the pathophysiology and its risk factors which increases the morbidity need to be elaborately study.

## Pathophysiology of diabetes

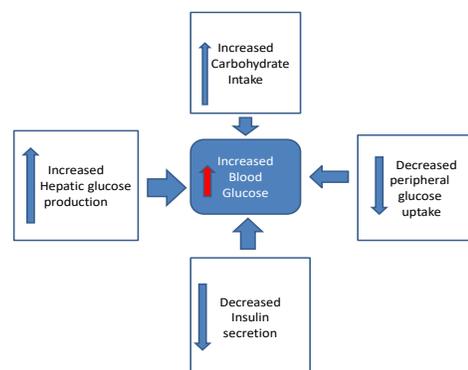
### Type 1 diabetes mellitus

Several factors that causes diabetes such as increased carbohydrate uptake or hepatic glucose production has been summarized in Fig. 1. Characterized by autoimmune destruction of insulin producing cells in the pancreas. The body's own immune system ,which normally fights harmful viruses and bacteria ,mistakenly destroys insulin producing cells such as islet or islets of Langerhans in the pancreas. When a significant number of cells are destroyed, produce little or no insulin. Causes of the presence of certain genes indicates an increased risk of developing type 1 diabetes. Exposure to viruses and other environmental factors may also leads to type 1 diabetes. When there is a deficiency in insulin leads to uncontrolled lipolysis and elevated levels of free fatty acids in the plasma, which suppresses glucose metabolism in peripheral tissues such as skeletal muscle. This impairs glucose utilization and insulin deficiency also decreases the expression of several genes necessary for target tissues to respond normally to insulin such as glucokinase in liver.

### Type 2 diabetes mellitus

In this dysfunction of the pancreatic  $\beta$ -cell occur, inadequate amounts of insulin and impaired insulin action through insulin resistance. Insulin resistance refers to when cells of the body such as liver, fat cells and muscle fail to respond to insulin. The plasma insulin concentration is insufficient to maintain normal glucose homeostasis. Insulin resistance and hyperinsulinemia eventually lead to impaired glucose tolerance. Inherited as an autosomal dominant trait, may result from mutations in glucokinase gene on chromosome. Although genetics and environmental factors such as excess weight and inactivity seem to be

contributing factors. Type 2 diabetes can be hereditary.



**Fig. 1:** Factors cause increase blood glucose level.

### Immune responses to hyperglycemic Condition

In search for the answer of why hyperglycemic environment in diabetic patients is more susceptible to infection. From earlier reported study, it was found that this situation is responsible for deleterious effects in immune defense mechanism. It may result due to changes in (a)leukocytes functions, (b)complement system and altered in microvascular responses (Fig. 2A, 2B)

#### Effects in leukocytes functions:

Hyperglycemic environment in diabetic patient may affects the leukocytes functions in many ways like decreasing chemotaxis, phagocytosis, adherence and bactericidal activity. Chemotaxis is considered as an important mechanism for mobilizing immune cells and phagocytic as an immune reaction at sites of infection, tissue injury [4]. From earlier study it has been observed that, chemotaxis is inhibited by hyperglycemic condition and this is reversed in case when treated in control insulin [5-7]. Reports shows in an animal models,

hyperglycemia caused impairment of phagocytosis in both monocytes and granulocytes and the immune dysfunction was partially reversed by insulin [8]. In another reports also shows that, in hyperglycemic condition glucose 6-phosphate dehydrogenase (G6PD) is inhibited reflects its antimicrobial action, also increases apoptosis of polymorphonuclear leukocytes and reducing polymorphonuclear leukocyte transmigration through the endothelium [9]. Many reports show that in both diabetics and in hyperglycemic environment, the bactericidal activity of neutrophils is decreased in environments. This may vary, however, with the organisms being investigated [10, 11]. Respiratory burst (sometimes called oxidative burst) is the rapid release of reactive oxygen species, plays an important role in the immune system. Report shows that high glucose concentrations in vitro cause inhibition of PMN respiratory oxidative burst. Result the decreased of intracellular pathogen lysis that occurs during hyperglycemia. Phagocytosis is also impaired by decreased oxidative burst generation in monocytes [8, 12].

**Effects in complement system:** It is a part of an immune system that is responsible for the enhancing the ability of phagocytic cells and antibodies to clear microbes. The stimulation of phagocytes, as a result of complement activation cascade cause clear of foreign and damaged material and inflammation to attract additional phagocytes, and activation of the cell-killing membrane attack complex. The complement system consist of more than 30 proteins and protein fragments, including serum proteins, and cell membrane receptors. The classical complement pathway, the alternative complement pathway, and the lectin pathway are the biochemical pathway that activate the complement system. The

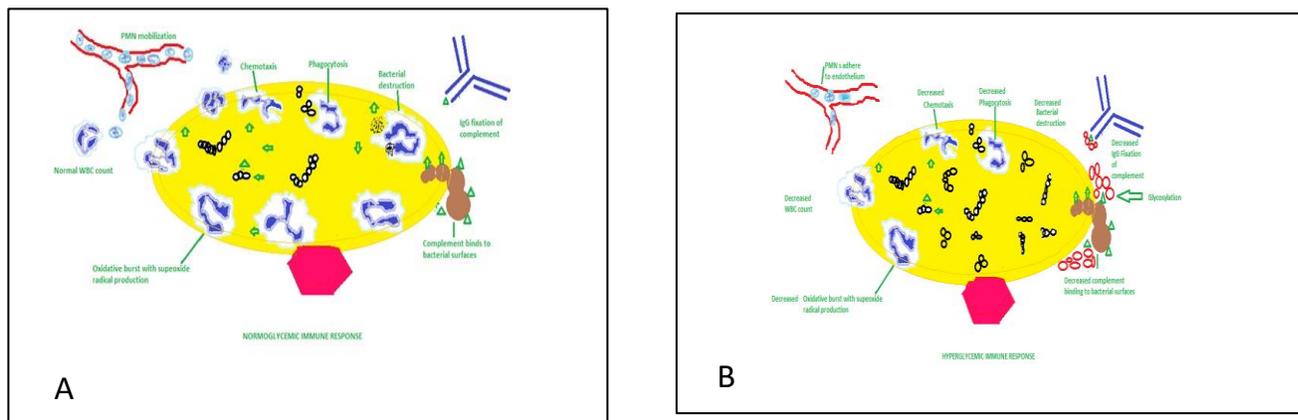
intricate complement system involved, human Complement component 4 (C4), which is a protein, originating from the human leukocyte antigen (HLA) system. It works for several critical functions in immunity, tolerance, and autoimmunity with the other numerous components. Furthermore, it is a crucial factor in connecting the recognition pathways of the overall system instigated by antibody-antigen (Ab-Ag) complexes to the other effector proteins of the innate immune response. For example, the severity of a dysfunctional complement system can lead to fatal diseases and infections.

From earlier reports it has shown deficiency of C4 component in diabetes [13]. The deficiency may be due to polymorphonuclear dysfunctions and reduced cytokine [14,15]. In another study, it was found that hyperglycemic conditions inhibit C3-mediated complement effects in bacterial infection and this is due to glycosylation of the C3 element, The conditions of elevated glucose cause C3 to undergo structural changes affecting the immune response in hyperglycemic environment [16,17].

**Altered Microvascular responses:** The effectiveness of an immune response depends not only on the proper activation, regulation, and function of immune cells, their distribution in diverse tissue microenvironments is also very important, where they encounter a number of stimuli and other cell types. Endothelial cells are responsible for these activities, which form specialized microcirculatory networks used by immune cells under both physiological and pathological circumstances. Both conditions are proinflammatory, leads to increased levels of TNF-alpha, IL-6, and IL-8. While inflammatory responses are

important in eradication of infectious agents, the resulting edema can lead to hypoxia as well as microvascular and macrovascular dysfunction. [18,19,20]. Reports also indicates that nitric oxide production is also hampered in hyperglycemic condition and as a result it cause failure of vasodilation which

may result in preventing phagocytes to reach the infection site/ target [21].



**Fig. 2:** Showing changes in immune responses due to hyperglycemic environment, A: Normoglycemic Immune Response B: Hyperglycemic Immune Response (picture taken and modified from Ashley M. Shilling et al., 2008)

### INFECTIONS IN DIABETES

In diabetes mellitus, there are some infections frequently arising and this has increased the risk of altered immune response due to hyperglycemia. There are number of rare but potentially fatal infections occur primarily or even almost exclusively in patients with diabetes. These include emphysematous urinary tract infections, Rhino cerebral mucormycotic, emphysematous cholecystitis, necrotizing fasciitis and malignant otitis externa (Table 1).

#### Malignant external otitis

It is an aggressive and potentially life-threatening infection of the soft tissues of the external ear and surrounding structures. Causative organism is *Pseudomonas aeruginosa*, begins with external otitis that progresses into an osteomyelitis of the temporal bone. Spread the diseases outside

the external auditory through Santorini and osseocartilaginous junction. It occurs more in old diabetic and immune-compromised patients (Fig 3). Facial paralysis (Fig. 4) is occurred in 50% cases. The best diagnostic method is the magnetic resonance imaging. [22-23] (<http://www.drmmkotb.com>)

#### Rhino cerebral mucormycotic

It is a rare opportunistic and invasive infection. This infection occurs in 50% of the cases approx. Individual with DM due to greater availability of glucose causes



**Fig. 3** Malignant otitis externa



**Fig. 4** Paralysis especially facial nerve

Mucormycotic. Caused by fungi of the class Zygomycetes. Classical triad are paranasal sinusitis, ophthalmoplegia with blindness, unilateral proptosis with cellulitis Black necrotic eschar in the nasal cornets characteristic sign. Facial or eye pain and necrotic wound of the palate of the nasal mucosa may occur. commonly affects individuals with diabetes and those in immunocompromised states [23-24]

#### **Emphysematous urinary tract infections**

Emphysematous cystitis and pyelonephritis consider to be rare but most dangerous complications of common urinary tract infection. Those who has poorly controlled diabetes suffered from this rare infection, raising chances more than 95% of patients with an emphysematous urinary tract infection. The causative organism is E.

**Table 1. Infectious Disease in Diabetic Patients**

#### ***Gastrointestinal and liver infections***

*H. Pylori* infection  
Oral and esophageal candidiasis  
Emphysematous cholecystitis  
Hepatitis c  
Hepatitis b  
Enteroviruses

#### ***Respiratory infections***

*Streptococcus pneumoniae*  
Influenza  
H1n1  
Tuberculosis

#### ***Urinary tract infections***

Acute Pyelonephritis  
Asymptomatic bacteriuria  
Fungal cystitis  
Renal Emphysema  
Emphysematous cystitis  
Perinephric abscess

#### ***Head and neck infections***

Invasive external otitis  
Rhinocerebral mucormycosis

#### ***Skin and soft tissue infections***

Pyomyositis  
Malignant External Otitis  
Foot infection  
Necrotizing fasciitis  
Fournier's gangrene  
Bacterial infections:

- Styes
- Boils folliculitis
- Carbuncles
- Infections around the nails

Fungal infections

- Ringworm
- Jock itch
- Vaginal yeast infection
- Athlete's foot

#### ***Other infections***

Human immunodeficiency virus  
Oral Infections

- Gingivitis
- Periodontitis

Surgical Infections

Coli and constitute in 70% of cases [25] Suffering patients might have, fever to persists despite adequate antimicrobial therapy. With the help of CT scan gas formation in the pyelum or bladder wall can be diagnosed. Hyperglycemia result Gas

formation and impaired blood supply, in combination in the presence of gas forming bacteria, facilitating anaerobic metabolism. For emphysematous cystitis Antibiotic treatment alone is mostly enough but Emphysematous pyelonephritis should be treated with adequate antibiotic treatment in combination with either percutaneous drainage or nephrectomy. Mortality is between 7 and 13%, despite adequate and immediate treatment.

### **Emphysematous cholecystitis**

It is a rare infection affecting men. About 40% diabetic patients experienced emphysematous cholecystitis. The diagnosis is usually made with (ultrasound, x-ray or CT scan). Causative organism are *Clostridium species*, *E coli*, and *Klebsiella species*. In case of emphysematous cholecystitis, rapid cholecystectomy should be performed. In case of an unacceptably high surgical risk, percutaneous drainage can be considered. Mortality of emphysematous cholecystitis is estimated to be around 15%, compared to 4% of patients with non-emphysematous cholecystitis.

### **Necrotising fasciitis**

It is another rare soft tissue infection. it is fatal in 20-40% diabetic patient [25]. About 70% of patients with necrotising fasciitis has diabetes mellitus. Necrotising fasciitis of the genital, perineum and perianal region is also named 'Fournier's gangrene.' The clinical presentation is erythematous skin discoloration and low grade fever. Pain may be disproportionately severe for the physical findings. When crepitus and hematologic bullae appear a few days later, the disease is likely to be fatal. Rapid intervention with antimicrobial treatment in combination with extensive surgical intervention is essential. Causative organism is *Staphylococcus aureus*, beta haemolytic streptococcus

bacteria, and vibrio bacteria are most common.

### **CONCLUSION**

Diabetic patients are compromise of infectious disease due to hyperglycemic environment, which suppress the immune response resulting in number of fatal infectious diseases which commonly occur in diabetic patients like malignant external otitis, Rhinocerebral mucormycosis, and gangrenous cholecystitis, this increases the chances of morbidity and mortality. Thus, diabetic patients' complication is to be identify promptly to control the hyperglycemic environment and possible treatment can be provided. But still the extent diabetic patients increase the risk of infections is still controversial due to lack of controlled clinical studies. Thus, more clarification is required to understand the immunopathogenic mechanism related to diabetes patients.

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