

# Diabetes mellitus (DM) leading to immune dysfunction

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**Abstract:** Infections are more common in diabetic patients than in non-diabetics. Immune deficiencies are one of the predicted reasons for this increasing incidence of infections. No changes in adaptive immunity have been reported in diabetes individuals Apart from some reduced cellular responses in vitro. Many abnormalities in humoral innate immunity have been reported in diabetic patients. However, the practical significance of these observations is unknown. In terms of cellular innate immunity, most studies suggest that diabetes polymorphonuclear cells and diabetic monocytes/macrophages perform less than control cells. In general, improved DM control leads to improvements in these cellular processes. Furthermore, in a high glucose environment, some microbes become more pathogenic. An enhanced adherence of microorganisms to diabetes cells relative to nondiabetic cells is another mechanism that might contribute to an increased occurrence of infections in diabetic individuals. *Candida albicans* has been characterised in this manner. This occurrence might be explained by the receptor's carbohydrate content.

**Keywords:** polymorphonuclear, diabetes mellitus, monocyte, adaptive immunity, cellular response.

## Introduction:

Diabetes patients are more prone to infection as compared to that of non-diabetic patients [1]. The most common form of infection seen in diabetes patients is ketoacidosis. It may be due to the deposition of microorganisms in diabetic cells which will ultimately lead to the weakening of the immune system. The immune system is broadly classified into two types namely [2, 3].

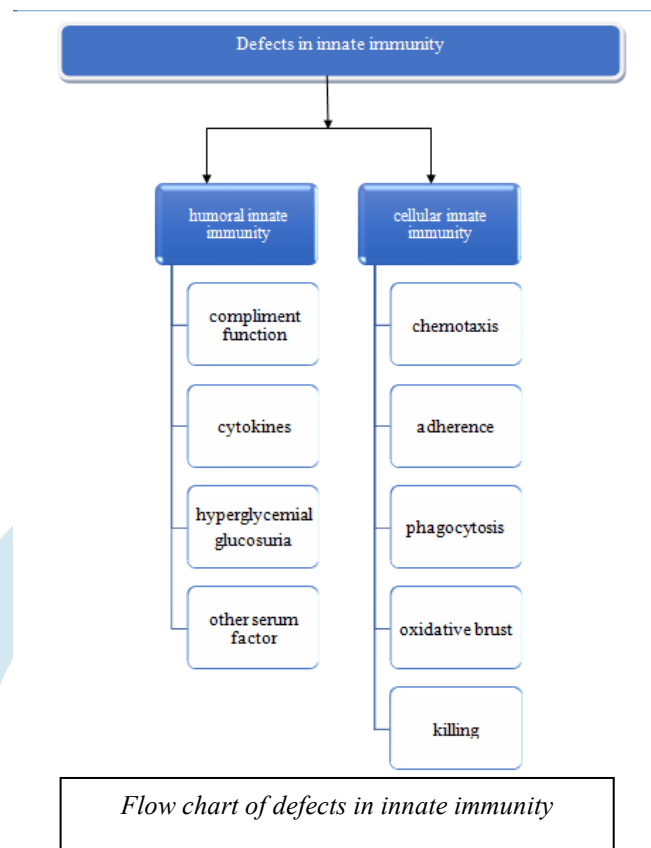
1. Innate immune system
2. Adaptive-humoral immune system/Adaptive-cellular immune system

**A. Adaptive-humoral immune system:** In these the patients with DM shows normal serum antibody concentration and they show a positive response to pneumococcal vaccine and there were no differences in the immunological response to intramuscular hepatitis B immunisation between children with type 1 diabetes and controls [4].

**B. Adaptive-cellular immune system:** In the lymphocytes of poorly managed diabetes suppression of the proliferative response to various stimuli has been found.

In both type 1 and type 2 diabetes, an aberrant delayed-type hypersensitivity reaction has been recorded. However, persons with diabetes are not susceptible to mycobacterial infections or *Pneumocystis carinii* pneumonia compared to those without diabetes. So the issue remains as to how significant these in vitro disruptions are in vivo [5-7].

From these facts, it looks like variations in innate immunity and microbe adhesion to diabetes and nondiabetic cells are more essential in the aetiology of the greater occurrence of infections in these individuals. The detailed study of the topic has been done in this article.



### Humoral innate immunity

**Complement function:** The study has been conducted on type 1 diabetic patients (86) and non-diabetic patients. The results of the study show that 22 patients with DM had shown a decreased level of serum factor 4 concentration (C4). The non-diabetic patients also show a decreased level of C4 factors (DR3 and DR4 are the antigens linked to genes encoding C4) which can make a conclusion that C4 deficiency is not a risk factor; hence it does not play a significant role in high-risk infection in DM patients [8].

**Cytokines:** Investigations involving diabetics' whole blood, peripheral blood mononuclear cells (PBMCs), and isolated monocytes must be separated into investigations with and without stimulation. Without stimulation, tumour necrosis factor K (TNF- $\alpha$ ) concentrations in type 1 diabetes patients, interleukin (IL) 6 concentrations in type 2 diabetes patients, and IL-8 concentrations in type 1 and 2 diabetes patients were investigated. Diabetes patients had higher resting levels of TNF- $\alpha$ , IL-6, and IL-8 than nondiabetic controls [9-11].

Studies involving PBMCs and isolated monocytes from diabetes patients after stimulation indicate the following results: in one research, diabetic PBMCs secreted less IL-1 in response to lipopolysaccharide (LPS), although the TNF- $\alpha$  response was the same as in control cells. In another investigation, monocytes from DM type 1 patients produced considerably less IL-1 and IL-6 after stimulation with LPS, but there were no differences in TNF- $\alpha$  concentration when compared to monocytes from DM type 2 patients and nondiabetic controls. After a 24-hour incubation period, the majority of the TNF- $\alpha$  may have already vanished. Because neither glucose nor insulin had any influence on IL-1 or IL-6 production in isolated monocytes, the reduced production following LPS stimulation appeared to represent an intrinsic cellular defect of diabetes cells. It is probable that diabetes cells' increased resting value induces tolerance to stimulation, resulting in reduced cytokine outputs following stimulation. This behaviour has already been observed in non-diabetic cells. Studies of cytokine excretion by nondiabetic individuals' PBMCs following the addition of varied glucose concentrations yielded equivalent findings to diabetic cells [12-14].

Unstimulated nondiabetic monocytes demonstrated an enhanced TNF- $\alpha$  and IL-6 response after the addition of varied glucose doses, according to one research [15]. Another study [16] discovered that following pokeweed mitogen activation, reduced levels of IL-2, IL-6, and IL-10 were detected with the addition of glucose. The above-mentioned tolerance induction might potentially explain these findings. In other words, the presence of glucose increases resting cytokine synthesis; but, after stimulation, this cytokine production is reduced relative to the state without glucose. Advanced glycation end products (AGEs), which are products of glucose and lysine or arginine residues, are another chemical that may play a role in increased baseline cytokine release. In poorly controlled diabetes individuals, AGE production is enhanced [17]. Several investigations have demonstrated that binding of these AGEs to nondiabetic cells without stimulation causes an increase in cytokine output, suggesting that the higher synthesis of these AGEs in diabetics may be responsible for the increased baseline cytokine release.

**Hyperglycemia/glucosuria:** DM patients are more prone to hyperglycemia. Certain microorganisms are more aggressive in the hyperglycaemic environment. For example, *Candida albicans*, for example, produces a surface protein with high similarity to the receptor for complement factor 3b (CR3). Microorganisms are normally opsonized by the attachment of complement factor 3b (C3b). Phagocytizing cells' receptors recognise this bound C3b and bind, commencing ingesting and death. The production of *C. albicans*' receptor-like protein in a hyperglycemic environment increases, resulting in inhibition and competitive binding of complement-mediated phagocytosis. Another illustration is the occurrence of glucosuria in people with poorly controlled diabetes. Bacterial growth in several *Escherichia coli* strains is promoted by glucosuria which may contribute to the higher prevalence of urinary tract infections in diabetes patients [18-19].

As a result, it appeared that proper diabetes management might reduce the aggressiveness of several harmful microorganisms.

**Other serum factors:** Zinc is a commonly discussed component in the DM. Type 1 and type 2 DM has shown Low plasma zinc levels. In another investigation, no differences in zinc levels were detected between diabetic and nondiabetic patients. In vitro, studies have shown an interruption in lymphocyte response and a decrease in chemotaxis in diabetic PMNs due to zinc deficiency. Other in vitro experiments with nondiabetic individuals' PBMCs revealed that zinc increased LPS-induced excretion of pro-inflammatory cytokines. From these opposite epidemiological studies, it can be stated that the role of zinc in causing infection is still unknown [20-21].

### Cellular innate immunity – PMNs

**Chemotaxis:** The chemotaxis of diabetes patients' PMNs was shown to be considerably lower than that of controls [22, 23]. However, we were unable to establish this difference in our investigation, which compared PMN function in women with DM and asymptomatic bacteriuria to nonbacteriuric diabetic women and healthy controls. Serum from healthy controls was utilised in all of the experiments. The above-mentioned studies' inconsistent results may be explained by the varied stimulation of the PMNs and variances in patient characteristics. There was no association identified between glucose concentration or haemoglobin A1C level and chemotactic reactions, while one research did demonstrate a further decline in chemotaxis in hyperglycemic individuals. Interestingly, one of the other investigations found that the chemotactic responses of PMNs did not change following incubation with either glucose or insulin, but reverted to normal after incubation with both. Because the majority of PMN functions are energy-dependent activities, enough energy generation is required for optimum PMN performance. To create energy, glucose requires insulin to reach the PMNs, which may explain why the chemotactic response improves following the addition of these two chemicals [24, 25].

**Adherence:** Incompatible results on the in vitro adherence of diabetic PMNs without stimulation have been published. On the other hand, results from stimulation show no differences in diabetic and control PMNs. There was no association between plasma glucose and adherence. However, once hyperglycemia was addressed in a limited number of DM type 1 and DM type 2 patients, the reduced adhesion of PMNs to nylon fiber columns increased. Of course, adhesion to nylon fiber columns differs from adhesion to endothelial cells as the first stage in the inflammation response. However, improved DM management appeared to increase the host response [26].

**Phagocytosis:** When compared to PMNs from controls and diabetes patients' PMNs had the same and a lower phagocytotic capacity. The mean HbA1c concentration was lower in individuals who did not have impaired phagocytosis than in those who did. An inverse association between HbA1c levels and the phagocytotic rate was shown in a study. Another study found that after 36 hours of normoglycemia, the reduced phagocytosis improved but did not return to normal. As a result, it appears that phagocytosis is impaired in PMNs isolated from poorly regulated individuals and that better DM control leads to increased phagocytotic activity [27, 28].

**Oxidative burst:** CL has a strong correlation with antibacterial activity and may be used to assess phagocytotic capability. CL in diabetic patients' PMNs was greater or the same at baseline as in controls. These experiments also revealed that the CL of diabetic PMNs was lower complying with stimulation than that of control PMNs. It is likely that the response of diabetic PMNs to stimuli was reduced by the greater resting of CL. We found no variations in CL following stimulation between diabetes patients and controls in our investigation. However, in general, the patients in our research were more controlled than those in previous trials, which may explain the disparity in outcomes [29-30].

**Killing:** The killing function of diabetic PMNs was shown to be diminished in all investigations that employed *Staphylococcus aureus* as the microbe, but not in those that used *C. albicans* killing as the method of measurement. In one trial killing was hindered that employed nondiabetic serum for opsonization, but not in another.

As a result, we cannot make any conclusions about the influence of nondiabetic serum on the death of diabetic cells based on this research. Although some investigations have shown that bactericidal activity improved but did not normalise after obtaining normoglycemia, no link was established.

**Adherence:** Diabetic individuals are commonly infected with *Candida albicans*. Because infection is usually preceded by colonisation, researchers looked at whether risk variables enhanced the probability of *Candida* carriage in diabetes

individuals. Lower age and a higher HbA1c level were risk variables for oral *Candida* carriage in individuals with type 1 diabetes. Continuous denture use and the presence of glucosuria enhanced the probability of *Candida* carriage in DM type 2 patients, and the average number of cigarettes smoked per day was connected with *Candida* carriage in both DM types 1 and 2. Cameron et al. collected lipids from human buccal epithelial cells and discovered that certain *C. albicans* strains bind to fucose-containing lipids while other *C. albicans* strains bind to N-acetylgalactosamine-containing lipids isolated from human buccal cells using chromatogram overlay experiments. The authors conclude that the presence of many adhesin-receptor systems adds to *C. albicans* pathogenicity [31]. The carbohydrate composition of receptors is most likely essential in infection susceptibility. It has been demonstrated that seriously unwell patients have lower levels of galactose and sialic acid on their buccal cells than slightly ill patients and healthy controls. The researchers speculated that these receptor alterations may promote microbe adhesion and contribute to the high incidence of Gram-negative bacteria colonisation in these individuals' respiratory tracts.

This mechanism of enhanced adherence caused by a change in receptor carbohydrate content may also be evident in diabetic individuals. Buccal cells from 50 diabetes patients had higher *C. albicans* in vitro adhesion than buccal cells from controls. This patient group also had a considerably greater frequency of *Candida* infection, but not *Candida* carriage. However, no correlations were discovered between the frequency and quantity of *Candida* and age, duration, regulation, or type of diabetes. This enhanced adherence to diabetic cells may also have a role in the adhesion of other microorganisms, such as *E. coli* to uroepithelial cells, which would explain the higher occurrence of infections in DM patients [32].

### Conclusion:

Disruptions in cellular innate immunity contribute to the aetiology of the higher incidence of infections in diabetes patients. In general, improved DM control leads to improved cellular function. A second crucial mechanism is the microorganism's enhanced adhesion to diabetic cells. Furthermore, in a high glucose environment, some microbes become more pathogenic.

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