# IMMUNODEFICIENCIES IN DIABETES AND MYCOBACTERIAL INFECTIONS

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## DIABETES MELLITUS AND TUBERCULOSIS – THE IMMUNOLOGIC INTERACTION

Diabetes mellitus (DM) is being increasingly documented even in developing countries. Both insulin dependent (IDDM) and non-insulin dependent (NIDDM) are associated with a variety of genetically determined complications. In addition, infections have been listed as an important complication amongst diabetics. Diabetics particularly IDDM and the 'poorly controlled' patients are considered as immunocomprised, though it is not easy to clearly characterise the immunologic deficiencies. An observation beyond dispute is the increased susceptibility and severity of infections in diabetic subjects. Root made the classic observation that tuerculosis (TB) was ten times more common in juvenile diabetics and in those with longer duration of diabetes mellitus[1]. Recently this fact has been reemphasised by the Center for Disease Control, which recommended isoniazid chemoprophylaxis is tuberculin positive diabetics[2]. A recent study in 1990, also documented higher prevalence of tuberculosis in 9% of IDDM vs 2.7% in NIDDM subejcts in Tanzania [3]. The NIDDM's do not lag behind. Patel in a large series of 8793 cases of diabetes mellitus, in Mumbai, noticed TB in 5.9% of Niddm's [4].

## PATHOGENESIS OF TB [5,6,7]

The basic principles of pathogenesis of tuberculosis are well known. A brief recapitulation of the pathologenesis in the light of recent advances in immunology is helpful for the better understanding of the disease process in the immunocompromised hose. The attempt, albeit oversimplistic, would never-theless be a reasonable conceptual framework to interpret the problem in special situations such as diabetes mellitus. In a large majority of subjects infected with tubercle bacilli, it is contained and immunity develops with a recall ability to mount a good response on second infection, when it occurs. In some subjects it leads to either progressive disease soon after or long after into post primary type. The post primary is characterised by granulmotous or cavitary lesions. A rapidly progressibe pneumonia or wide-spread dissemination is a frightening one, predominant in immunocompromised hosts. The classic example of immunodeficiency epidemic today is AIDS. As already emphasised, it is not clear, due to lack to information in the available literature, what kind of immunocompromise occurs in diseases such as DM. The virulence of mycobacterium depends on it's abolity of bat-off the salvoes of the host immunity. The destruction in host tissues is due to inflammatory responses of the host. Polymorphs are the frontline defenders who engulf but breakdown without a kill-effect. Their death moves the macrophages to pin down the mycobacteria and wall them off. Central to this mechanism is the lymphocyte. The lymphocytes are mainly of two types – T and B. The T lymphocytes are macrophage-activators and memorisers of immunity, The T lymphocytes are divided into helper (Th4 or CD4) and suppressors (Th8 or CD8). CD4 lymphocytes are further subdivided into Th1 and Th2 based on the type of cytoknies realeased. Th1 cells secrete interleukin-2(IL-2) and gamma interferon (IFN-g ). The h2, on the other hand, secrete interleukin-4 (IL-4) and IL-5. Th1 cells predominantly confer protective immunity while Th2 help the delayed type skin response leading to antibody production. It may not be totally out of context to summarise the various cytokines in relations to immune cells. (Table 1).

**Table 1: Cytokines produced by various immune cells**

| Cytokine | Macrophage | Th1 | Th2 |
|---|---|---|---|
| IL-2 | - | + | - |
| IFN-γ | - | + | - |
| Lymphotoxin | - | + | - |
| IL-4 | - | - | + |
| IL-5 | - | - | + |
| IL-6 | + | - | - |
| IL-10 | + | - | - |
| GM-CSF | + | + | + |
| TNF | + | + | + |

The clinical outcome of infection depends on the efficacy of cell mediated immunity. Patients with

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HIV or renal failure are at a higher risks for TB, while patients with multiple myeloma, which is associated with a humoral defect, do not show increased predisposition to TB. Macrophages and T lymphocytes are the chief managers of the show. Neutrophils, natural killer (NK) cells and eosinophils also demonstrate antimycobacterial properties without bactericidal activity. Among the T cells, the Th (CD4) cells are the most important. The current evidence though not above dispute, strongly favours selective role of Th1 cells in a good immune response against TB. In contrast to Th1 cytokines, the Th2 cytokines, IL-4 was observed to deactivate macrophages and block T cell proliferation. Experimental evidence suggests that alveolar macroophages ingest mycobacteria and product IL-12, which favours development of Th1 response. If the interplay between macrophages achieve a total kill, the T cells are not exposed to mycobacterial antigens and the tuberculin test may be negative. Gamma delta T cells may predominate in the initial inflammatory response, but they may not contribute to memory system. Protective Th1 response contributes to delayed type hypersensitivity which is also associated with a protective response. Some patients develop extensive disease, caviation and hyperglobulinaemia. This may be due to domination of macrophage cytokines or immunosuppressive Th2 response. Miliary TB reflects a defective Th1 response and predominance opf IL-4, IL-10 and TGFb produced by Th2 cells and macrophages. Reactivation of healted foci occurs in 5-10% of infected prople. When it is associated with Th1 response, mild pulmonary or pleural TB occurs. On the other hand, if the response is mainly macrophage or Th2 type, extensive disease occurs.

A special situation associated weth severe immunocompromise is the HIV patient, where the risk of primary and reactivation TB is high. The CD4 cell function and antimycobacteria activity, perhaps,deteriorate even before the cell counts fall. Evidence also suggests that may accelerate HIV infection through increased TNF production stimulated by mycobacterium tuberculosis. Th1 mediated delayed type hypersensitivity which has a protective benefit is also impaired by HIV, malnutrition and steroid therapy. T cells only recognise the antigen when it is on the surface of a body cell. The CD4 and CD8 cells receive information when the surface marker of a cell with antigen containing intracelluar parasite, recognise that it is not a self cell. The surface markers of self belong to a group of molecules known as the major histocompatibility complex. The CD4 cells recognise the antigen plus MHC Class-II surface markers of the macrophages and start clonal expansion and lymphokine production. HLA Class-II D and DR2 genes have been implicated in the development of smear positive pulomonary TB. Studies have shown that Class-II HLA-DR genes may determine the Th1 or Th2 response. The genetic characters of host seem to be as important as the virulence of the mycobacteria in determining the pathology. Whether the polygenic disease of diabetes mellitus has increased genetic susceptibility, irrespefctive of glycaemic control, needs to be examined.

## STUDIES ON IMMUNE DEFICIENCIES IN DIABETES MELLITUS

Very few studies have been conducted on immunological function in relation to increased susceptibility to infections in diabetes mellitus. Several potential mechanisms have been postulated for increased proneness to infections in diabetic patients. It is however not easy to assign the relative importance. While long term complications such as neuropathy etc., can indirectly lead to trauma, neurogenic bladder etc., attempts to crystallise defects in the immunologic defence in the light of recent concepts have been very few. Broadly the phagocyte function and the cell mediated immunity which are important in pulmonary infections are reviewed as follows.

### Phagocyte in diabetes mellitus

Numerous studies on leucocytes have indicated deficiency in diabetic patients. Diabetic ketoacidosis on correction resulted in improved phagocyte migration [8]. Bybee and Rogers additionally had shown that phagocyte functional defect was not confined to ketoacidosis but also occurred in poorly controlled diabetics. Good control of diabetic state reversed the phagocyte defect. [9]. Another interesting observation, which suggested a possible genetic determination of the phagocyte defect was that of Molenaar, who studied the leucocyte function amongst the family members of diabetics[10]. The importance of serum factors was highlighted by Bagdade et al., 1974, who documented reduced function of phagocytes from normal subjects on exposing them to diabetic sera. Interestingly, control sera improved the phagocyte function of diabetic leucocytes in the other limb of the experiment. It was therefore hypothesised, that serum factors played an important role in the phagocyte function of the diabetics[11]. Recently in 1998, Saeed and Castle studied human neutrophils by a chemiluminescence assay in the presence of high levels of acetoacetate. The found diminished

phagocyte activity and inhibition of myhelo-peroxidase [12].

Certain serum factors may competitively bind neutrophil receptors thereby preventing complement mediated phagocytosis. Eliminiation of circulating immune complexes is also poor amongst diabetics [13]. Chemotaxis of neutrophils was found to be less in diabetics in a well controlled study of Mowat and Baum [14]. The greater spread of infection, poor granuloma formation and reaction and reactivation of old foci may be explained by the observation of Sheldon and Bauer that granulocytic phase of inflammation was retarded and diminished [15].

## CMI in Diabetes

Cell mediated immunity (CMI) is a very important arc of host immunity. Assessment of lymphocyte transformation in response to phytohaemagglutinin showed a decrease in diabetics with poor control. In none of the controls and well-managed diabetics, an inherent defect of the T cells could be documented [16]. The poor glyucaemic controls as the lone determining factor for impaired CMI was questioned by Casey et al., who demonstrated poor response to microbial antigen in lymphocytes of diabetics with out any association with glycaemic controls [17]. Supportive to the above observation was the T-lymphocyte immunocompetence in the rat model of IDDM[18]. Tsujino et al., recently studied lymphocyte subsets, T cell, B cell CD3+56+by flow cytometry in 18 diabetic males and demonstrated a decrease in the CD3+56+lymphocytes when compared with controls [19]. Cytokines are the products of lymphocytes and mononuclear cells which reflect the activated status of cells. Tsukaguch et al., compared tuberculous diabetics with controls. Interleukin-1b , TNF-a and IL-6 were measured in the peripheral monocytges. IL-1, TNF, IF-6 production was significantly lower in diabetics with TB than in those with TB alone. Furthermore, IL-1 and TNF were lower in poorly controlled diabetics. There was also an inverse association between TNF and glycosylated haemoglobin levels in diabetics with TB[20].

The same group, recently, observed reduced levels of interferon gamma and interleukin-12 in diabetics with TB than in TB patients and controls Interferon gamma also showed an inverse ralationship with glycosylated haemoglobin (CD4a -b T lymphocytes were stimulated with live BCG in TB, BM and TB+DM patients)[21]. Reinhold et al studied effects of elevated glucose levels on both DNA synthesis and the production of interleukins, IL-2, IL-6, IL-10 in stimulated mononuclear cells from diabetics and normals. The effect was dose and time dependent [22].

The nonimmunologic mechanisms that may have a potential role, even though minor, are the damage to collagen and elastin of the lung due to their glycosylation resulting from chronic hyperglycaemia. The loss of elastic recoil in IDDM resembles accelerated aging and has been linked to collagen glycosylation and pulmonary angiopathy. Reduced elastic recoil leads to dynamic collapse of airways. Post mortem studies in diabetics have shown thickening of alveolar epithelial and capillary basement membranes, centrilobular emphysema and microangiopathy. These changes are likely to affect the pulmonary defence machanism in a subtle fashion [23,24].

## CONSLUSION

Diabetes mellitus is associated with more frequent and severe infections. Epidemiologic evidence supports more frequent and severe forms of tuberculosis in diabetic subjects. Experimental and human studies document phagocyte and cell medicated immune dysfunctions in diabetics. Host immune response is also contributory to the pathogenesis of tuberculosis., Hyperglycaemia, glycosylation, long term oxidative stress and genetic determinants may all contribute to the susceptibility and to the development of severe tuberculosis in diabetes. Immune dysfunction, which may lead to increased infections in diabetes, deserves further studies.

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