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EDITORIAL

Infections and diabetes

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Infections and diabetes illustrate the health problems facing India, and more. The two often coexist, making each other the worse for it. Subjects with diabetes have a greater frequency and severity of many common infections (urinary, pulmonary, soft tissue) whereas some rare infections are seen almost exclusively in the diabetic population viz. rhino-cerebral mucormycosis, malignant otitis-externa and emphysematous cholecystitis, cystitis, and pyelonephritis.

These infections should be sought in patients presenting with DKA and hyperglycemic hyperosmolar syndrome. Fournier's gangrene and infections of the foot occur predominantly in diabetics.

The increased susceptibility to infections and impaired wound healing is due to diminished vascularity, autonomic dysfunction, and abnormalities in cell-mediated immunity and phagocytic function. The common pathogens are *Escherichia coli*, *Klebsiella*, *Campylobacter*, and *Salmonella enteritidis*.

Infections may worsen glycemic control. Periodontal infection is linked with dysglycemia and cardiorenal complications.

Prevention from infection requires good glycemic control, good hygiene, and preventive vaccination.

Beside the well-recognized association of infection and diabetes, a recent study from India reported that the prevalence of hepatitis C in these subjects is higher; it was positive in 11 out of 192 (5.7 %) with a higher prevalence in men and in those with poorer glycemic control [1]. Similarly in an earlier study also from India, hepatitis B virus was more common in subjects with acute viral hepatitis having diabetes (58.33 vs. 25.3 % in controls) [2]. In a multiple variable logistic regression analysis, acute hepatitis B and diabetes were shown to be related to severe hepatitis.

Interestingly, *Helicobacter pylori* infection was higher in subjects with diabetes (*n* 62; 77.5 %) compared to controls (*n* 62; 77.5 %). It was correlated with poorer glycemic control, suggesting that chronic inflammation with the infection may be associated with subsequent development of insulin resistance [3].

Urinary tract infection is commonly observed in diabetes. Among Indian subjects with culture-positive urinary infection, nearly 30 % were asymptomatic. Diabetes was associated with a higher prevalence of pyelonephritis and with poorer glycemic control. In descending order, cultured pathogenic bacteria were *E. coli* (64.6 %), *Klebsiella* (12.1 %), and *Enterococcus* (9.9 %). Extended-spectrum beta-lactamase-producing *E. coli* was more common in diabetes [4]. With clinical introduction of antidiabetic agents acting through inducing glycosuria (SGLT2 inhibitors), counseling about genital hygiene must be integrated to reduce the risk of genital and urinary infections.

The enormous physical and financial burden of diabetic foot infection has been highlighted in a recent journal editorial [5]. The current issue describes diabetic foot involvement from Saudi Arabia [6] and China [7] and an uncommon bacteriological infection [8]. In India, smoking and barefoot walking are common underlying factors in foot complications among persons from both urban and rural areas [9], which are preventable. Recurrent infections are also a major burden [10], which must be tackled by proper education about foot care [11].

In a recent prospective study from Varanasi, Singh et al. showed that in 62 consecutive subjects with foot involvement,

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32 % had mono microbial infections; 35.5 %, poly microbial; and 21 %, sterile culture [12]. Of isolated bacteria, 68 % were gram-negative and 32 %, gram-positive. *E. coli* were the commonest isolate, showing sensitivity to piperacillin/tazobactam. A study from a different center also reported that gram-negative bacteria were more common in diabetic ulcers, in contrast to nondiabetic ulcers which harbored gram-positive bacteria [13]. Most of the multidrug-resistant strains produced biofilms, which along with poor immune response may account for poor wound healing.

Insights into biochemical pathways for diabetic ulcers are likely to identify newer therapeutic targets. Considering that heat shock proteins (HSPs), which are inducible stress proteins expressed in response to stress, play a role in wound healing, their circulating levels were measured in subjects with diabetic foot ulcers. Elevated levels of both HSP 70 and HSP 47 were observed in diabetic foot ulcer, suggesting it could be employed as a biomarker [14]. HSPs could also play a role in wound healing, and an inadequate response may contribute to foot ulcers. In order to evaluate their role in pathogenesis, a differential expression of HSPs and their downstream molecules were studied in diabetic wounds. There was a significant downregulation of HSP70, HSP47, and HSP27, along with that of downstream molecules TLR4 and p38-MAPK [15]. Also contributing to poor wound healing is the toll-like receptor (TLR) family, which initiates inflammatory signaling. An analysis of differential expression of endosomal TLRs in diabetic wounds (both transcriptional and translational levels) showed that TLR7 and TLR9 were significantly upregulated in wounds from subjects with type 2 diabetes [16]. Thus, altered expression of endosomal TLR could contribute to poor wound healing in diabetes. Whereas growth factors (platelet-derived growth factor, transforming growth factor, and epidermal growth factor) are needed for repair of wound, healing is delayed by proteases including matrix metalloproteinase and serine proteases, often found in chronic wounds [17].

Involvement of the upper limb in diabetes is also more common. In this issue of the journal, Bujang et al. reported on the characteristics and outcomes of such involvement [18]. Necrotizing soft tissue infections of the upper limb often have diabetes as a contributing factor [19, 20]. Diabetic end-stage renal disease also contributes to upper limb infections that require surgical treatment; infections are often nosocomial, which should be initially managed by an empirical antibiotic cover against MRSA and gram-negative bacteria [21].

Tropical diabetic hand syndrome, first identified in Nigeria and later also reported mainly from African countries and India, refers to a 'localized cellulitis with variable swelling and ulceration of the hands, to progressive, fulminant hand sepsis, and gangrene affecting the entire limb' [22]. It is often preceded by minor hand trauma and is associated with poorly controlled diabetes, malnutrition, and neuropathy. Immediate admission followed by aggressive surgical intervention is mandatory. Prevention or early intervention is essential to avoid serious systemic complications.

Fungal infections, both localized and systemic, are more common in uncontrolled diabetes. India reports a high incidence of opportunistic mycoses such as invasive candidiasis, aspergillosis, and zygomycosis. Invasive zygomycosis in particular has been especially identified from the Indian subcontinent among subjects with uncontrolled diabetes [23]. Nosocomial blood infection in the critically ill with candida is common. In a retrospective analysis of ICU patients, among 144 episodes of candidemia, diabetes mellitus accounted for 50 % of cases of *Candida glabrata* [24]. Among culturally proven scleritis due to bacterial or fungal causes, diabetes mellitus was present as a risk factor in 17 % (7 out of 42 cases) [25].

Mucormycosis, an angioinvasive infection by filamentous fungi (class Mucormycetes), was reported in 38 patients from a tertiary care hospital over a 12-month period; diabetes accounted for more than 50 % of rhino-orbito-cerebral presentation [26]. There are reports of mucormycosis coexisting with pulmonary tuberculosis in subjects with diabetes [27]. Uncontrolled diabetes, a risk factor for mucormycosis [28], has been associated with involvement of the kidney also [29].

Primary cutaneous zygomycosis, often undiagnosed, is associated with diabetes mellitus [30]; when treatment is delayed, it is fatal [31].

Periodontitis is increasingly recognized as an etiological factor in insulin resistance syndrome and type 2 diabetes mellitus. In this issue, one article reports on the effect of BMP-2 on mineralization of periodontal ligament in vitro [32], and another evaluates the effect of treating periodontal infection on glycemia and circulating inflammatory markers [33]. Interestingly, a recent case-control study hypothesized that maternal periodontal disease during pregnancy could be associated with low birth weight [34]. Guidelines have been provided for judicious antibiotic prophylaxis in dental procedures, particularly in subjects with poorly controlled diabetes as an adjunct to primary treatment of dental procedure [35].

A confluence of clinical observations and basic research has resulted in evidence-based treatment protocols as well as newer treatment methods. In this issue, Asemi et al. describe the effect of probiotic supplements on various parameters in type 2 diabetes [36]. The ability of probiotic to modulate immune response led to the proposal for their possible use in treatment of diabetic foot ulcers [37].

On the horizon are exciting prospects for imaging techniques such as positron emission tomography in the diagnosis of infections. Labeled with ^{18}F fluorodeoxyglucose was employed as a radiotracer for inflammatory cells, particularly infections of the bones [38]. Similarly, injection of bacteriophage in the treatment of multidrug-resistant *Pseudomonas aeruginosa* has been proposed in an animal model,

particularly in immunocompromised situations [39]. Finally, there is an intriguing possibility for statin group of drug use in diabetes having the ability to reduce the prevalence of tuberculosis acting via lipid pathways [40].

These are exciting times for infectious diseases in diabetes mellitus. Just as molecular biology, genomics and related omics technologies are being employed synergistically with psychosocial approaches for stemming the diabetes pandemic so do similar approaches seem to be the way ahead for prevention and treatment of infections.

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