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Review Article

DIABETIC FOOT INFECTION IN INDIA

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ABSTRACT

Diabetic foot infection (DFI) is one of the most feared complications of diabetes mellitus especially in India due to large population having diabetes mellitus, social stigmata, poor education, negligence by the patient and society and lack of dedicated diabetic foot centers. Usually patients presented with polymicrobial infection having both aerobic and anaerobic pathogens. Gram positive cocci like Staphylococcus aureus, gram negative bacilli of Enterobacteriaceae family are the most common among the aerobes while Peptostreptococcus and Clostridium are most common among the anaerobes are involved in diabetic foot infections. However, the prevalence of multi-drug-resistance pathogens is alarmingly high and complicating the management of diabetic foot infections and also plays a huge role in the duration of hospitalization, morbidity, and mortality. So, the knowledge of the common bacterial pathogens implicated as well as their sensitivity play a significant role in preventing adverse prognosis of diabetic foot infection.

1. Introduction

Diabetes mellitus is increasing worldwide and it is one of the most challenging health care dilemmas in the 21st century[1,2]. Diabetes mellitus is characterized by hyperglycaemia due to defects in insulin secretion, insulin action, or both [3]. The incidence of diabetic foot infections (DFI) in persons with diabetes ranges from a lifetime risk of up to 25% in all persons with the diagnosis, to 4% yearly in patients treated in a diabetic foot center.

DFIs may present as cellulitis or infections (post traumatic or surgical), but are most commonly a consequence of ulcerations secondary to associated progressive peripheral polyneuropathy. These neurological problems are usually accompanied by peripherial arterial insufficiency and immunological disturbances. Developing a DFI is now the most common diabetes-related reason for hospitalization and lower extremity amputation [4]. The management of diabetes and its complications is becoming very much expensive gradually, which is seriously preventing the strengthening of the Indian health care system. Among the diabetic populations, lower income patients bear the highest burden of diabetes [5]. Diabetes consumes from 5% to 25% of the total income of an average Indian family on diabetic care and treatment [6].

Epidemiology of Diabetes Mellitus: It is also described as the ``global epidemic`` of the 21st century. In 2015, 415 million people over the world were estimated to have diabetes, and this number is projected to rise to 642 million by the year 2040. The worldwide prevalence of diabetes among adults over 18 years of age has risen from 4.7 percent in 1980 to 8.5 percent in 2014 (WHO). It is estimated that the global prevalence of diabetes has been increased from 4% in 1995 to 5.4% by the year 2025 [7]. India ranks second in the world with 65.1 million diabetic patients [8]. With the increase of population in India the number of people living with diabetes is predicted to rise above 109 million by 2035[9]. Hence, it has been labeled as ``The diabetic capital of the world``.

Foot infections are common in diabetic patients with prevalence as high as 25%. It is also estimated that it is the most common cause of admission of diabetic patients in the hospital. Diabetes foot ulcers (DFUs) are the leading cause of non-traumatic amputations worldwide [10].

There is a large regional and socioeconomic difference in the prevalence of type II diabetes in India. The prevalence of diabetes is lower in rural areas (3.1%) than in urban areas (7.3%) [11]. In one of the study done by Shahi et al in (2012) showed that out of 581 patients having diabetes alone, 42.16% belonged to rural areas and 57.83% were from urban areas. On the other hand, in the DFUs group 70.16% cases belonged to rural areas and 29.9% were from urban areas. The risk of DFUs was higher in patients of rural areas than in urban diabetic patients [12].

The diabetic foot

The definition of the diabetic foot has been described as infection, ulceration with destruction of deep tissues associated with neurological abnormalities and peripheral vascular disease [1,2]. Diabetic foot ulcers and amputation are the major adverse outcomes. The incidence of foot ulcers in diabetic patients varies between 2 and 6% in Western Europe and North America and between 19% and 29% in the Middle East. The EURODIALE study showed that there are marked regional differences throughout Europe regarding diabetic foot ulcer and amputation incidence [13]. In india, a prospective study by Jayaprakash et al showed that 9 percent reported foot ulcer at the time of the study [14].

The clinical profile of diabetic foot differs and is influenced by multiple factors like walking barefoot or wearing inappropriate

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footwear, faith in alternative system of medicine, illiteracy and the lack of training of physicians at primary care in the treatment of the diabetic foot [15]. Foot ulceration is preventable, and relatively simple interventions can reduce amputations by up to 80 percent. To prevent the development of foot ulcer, early detection of the foot at risk should be afforded a high clinical priority [16].

Microbiological pattern of Diabetic foot infection in India

Microbial profiles of diabetic foot infections are widely studied and differ in different regions across India and the world. DFIs are usually polymicrobial. Study from western India, about bacteriological analysis and clinical grading of patients with diabetic foot lesions revealed polymicrobial aetiology in 85% and monomicrobial aetiology in 14% patients. Staphylococcus aureus among the gram-positive and Pseudomonas aeruginosa among the gram negative were the predominantly isolated organisms. Among anaerobes, gram positive cocci were the predominant (69%) with Peptostreptococcus species being the leading isolate [17]. While study done in south India by Iyanar et al found that only 37% patients showed the polymicrobial infection and remaining 63% showed mono microbial infection. Pseudomonas aeruginosa (48.3%) is the predominant bacterium followed by Staphylococcus aureus (38%) and other bacteria. The anaerobic bacteria are also isolated from the diabetic foot ulcers. The Peptostreptococcus species (26.7%) are the predominant bacteria followed by other bacteria [10].

Study done in northern part of India by Singh et al (2018), a total of 158 organisms (155 bacteria and 3 fungi) were isolated and the result found in cases were mostly positive for polymicrobial growth (77%) as compared to controls. Predominant isolated bacterias were Gram-negative aerobes followed by Gram-positive aerobes. Anaerobic Gram-negative (3%) and fungal (3%) isolates were also seen [18]. However, gram positive organisms predominate the causatives in the western part of the world [19,20]. When we listed the individual microorganisms, S. aureus was on top, followed by P. aeruginosa, similar to other studies from same region [21]. The most common pathogen isolated was E. coli followed by S. aureus in a study from North India, but in other studies P aeruginosa has been reported most frequently [22]. In a study by Saseedharan et al [23] from Maharashtra reported 61.8% isolated bacteria belonged to Enterobacteriaceae family.

The role of fungal pathogens in DFI is less frequently studied. A study by Chellan et al [24] revealed that there is a high prevalence (27.9%) of fungal infection in deep tissues of diabetic lower extremity wounds with Candida parapsilosis topping the list. Nair et al (2015) reported the 127/250 patients (50.8%) had MDRO infected ulcers. Currently, there has been an increase in the incidence and prevalence of ESBLs. The prevalence of ESBL among Gram-negative isolates is low compared to that of Gadepalli et al [25]. The highest production of ESBLs was noted in E. coli followed by Klebsiella spp. These are contrary to the observation by Gadepalli et al., (2006) which shows maximum ESBL production in Proteus spp (65.3%).

Drug Sensitivity

In a study by Aiswariya et al from South India reported S. aureus with maximum sensitivity to vancomycin and linezolid (100%) followed by clindamycin (75%) [26]. MRSA rate in this study was 39.28%. Enterococci were fully sensitive to vancomycin and linezolid, followed by gentamicin (70.59%). Gram negative isolates were mostly sensitive to Imipenem (97.30%) followed by cefaperazone sulbactam (81.98), piperacillin tazobactam (75.68), amikacin (72.97) and gentamicin (66.67).

Singh et al (2018) reported Gram-positive isolates mostly sensitive to vancomycin, levofloxacin, gentamicin, amikacin, and tetracycline while they were mostly resistant to amoxyclav, erythromycin, ciprofloxacin, and cotrimoxazole. Two isolates were identified as MRSA (33.3%) and one as vancomycin-resistant enterococci (16.7%) among the isolates. Gram-negative isolates were mostly sensitive to cefoperazone-sulbactam, levofloxacin, colistin, aztreonam, and tetracycline. On comparing between the two groups, ESBL and carbapenemase producers were much more common among cases as compared to controls. Escherichia coli was the most common isolate for ESBL and carbapenemase production both in cases and controls. Pseudomonas was the next predominant ESBL and carbapenemase producer. All the fungal isolates were 100% sensitive to voriconazole and resistant to fluconazole. 50% of the C. albicans isolates were sensitive to amphotericin B, whereas C. tropicalis was resistant to both amphotericin B and fluconazole [18].

Jain et al [27] found that most of the Enterobacteriaceae culture isolates were sensitive to amikacin (90%), imipenem (89%), meropenem (84%), ertapenem (76%), and piperacillin-tazobactam (73%). Among these isolates, the Enterobacteriaceae family was resistant to the majority of antibiotics tested, except colistin, imipenem, amikacin, and meropenem, partially consistent with the results of other studies [28]. However, the non-fermenting Gram-negative bacterial culture isolates showed the following - amikacin (90%), imipenem (72%), meropenem (70%), and piperacillin-tazobactam (74%) sensitivity pattern. Other studies have shown different antibiotic susceptibility patterns, and in most, vancomycin and linezolid have shown good activity against the strains [28]. Benwan Al et al reported vancomycin as the most effective antibiotic for Gram-positive bacteria [29].

Study by Otta et al [30] and Suresh et al [31] also reported linezolid, teicoplanin, and vancomycin were the most sensitive drugs for Staphylococcus spp. , may be due to the high prevalence of MRSA strains. Other antibiotics having moderately effective for Gram-positive coverage were piperacillin-tazobactam, cefoperazone-sulbactam, netilmicin, and levofloxacin. In this study the isolates of Enterobacteriaceae family to be the most sensitive to cefoperazone-sulbactam and imipenem, while ofloxacin, gentamicin, amoxicillin-clavulanic acid, and cefotaxime were the most resistant antibiotics. Pseudomonas spp. similar to previous works Gadepalli et al., Umadevi et al [25,32] showed highest sensitivity to imipenem and piperacillin-tazobactam, but Acinetobacter spp. were the most notorious strains showing almost resistant to most of the drugs being used.

MRSA has been a pathogen of concern in patients with diabetic foot infection and influence the empirical management. The prevalence of MRSA, in India, is high approximately 56%. The prevalence rate of ESBL producing E. coli and Klebsiella pneumonia and MRSA was 60%, 57.1% and 58 % respectively [17].

In the treatment for multidrug-resistant gram negative bacteria Carbapenems are the effective; however, a rising number of carbapenemases (and thus, resistance) is increasingly being reported from different parts of the world [25]. Metallo-beta-lactamase has been described previously in P. aeruginosa isolates from diabetic foot infections [33]. NDM (New Delhi metallo-beta-lactamase) is the latest in the armamentarium of

car-bapenemases. NDM1 was first identified in isolates from a Swedish patient of Indian origin in 2008. NDM producers have been described in studies from various parts of the world; although, many reports seem to originate from the Indian subcontinent [34]. However, there is paucity of data about the prevalence of NDM among isolates from DFIs in India. Khan et al. found NDM producing Enterobacter cloacae and Klebsiella pneumoniae strains isolated in two patients with diabetic foot ulcers from India [35]. Samant et al [36] described Providencia rettgeri strains harbouring blaNDM-likein 4 patients with diabetic foot ulcers from India for the first time.

Treatment

Management of diabetic foot ulcer is a multidisciplinary approach. It involves the following aspects [37]

- mechanical control
- wound control
- microbiological control
- vascular control
- metabolic control
- educational control

The treatment of the infected diabetic foot depends on its severity. Conservative treatment includes control of diabetes with human insulin along with antibiotics with wound debridement followed by dressing. Split skin grafting, disarticulation, below knee amputation, and above knee amputation were the other modes of treatment. The risk of lower extremity amputation is 15 to 46 times higher in diabetics than in persons who do not have diabetes mellitus [10].

Diabetic foot ulcers are a source of major suffering and cost. Only two thirds of these ulcers are expected to heal [38], the median time to healing of all ulcers is approximately 6 months. Almost 90% of the patients had infection with major amputations accounting for 29.1% and minor amputations for 70.9% of total amputations. Prevalence of neuropathy was high at 82%; 35% had peripheral vascular disease [39]. In those living in southern India, it was found that the prevalence of neuropathy (15%) was found to be higher, which is considered to be an important risk factor for diabetic foot infections; by comparison, it was lower among the northern Indians (9%). However, the prevalence of PVD was found to be equally common among both northern and southern Indians. Proper foot care practice was found to be lacking in around 65% of the study population, which also could be one of the causes for increased prevalence of foot infections. Longer healing time occurred when aerobic pathogen Pseudomonas and anaerobic pathogens were present (136.1 ± 28.6 and 136.4 ± 34.7 days, respectively) [40]. Patients with neuropathy and PVD have recurrent infections, around 53%.

Observational studies suggest that 6%-43% of patients with diabetes and a foot ulcer eventually progress to amputation [41]. Most of the foot problems associated with diabetes in India are neuropathic and infective rather than vascular in origin as in developed countries [42]. Among the patients who underwent major amputations, more than 50% underwent below knee amputations and 11.9% above knee amputations. Out of total amputations, over half were toes and rays amputation. Claw toes was seen in 64% of patients.

Initiatives to Manage Diabetic Foot Burden in India

In India, by implementing preventive strategies (intensive management and foot care education) were helpful in preventing newer problems and surgery in diabetic foot disease [43]. Recent study showed that recurrence of healed ulcers occurred in only one sixth of patients and amputations in just 1% of patients.

A study conducted by Viswanathan et al [44] determined the impact of intensive foot care education strategies for type 2 diabetic foot disease helpful in preventing newer problems and surgery for foot disease. It was found on follow-up, that 57% strictly followed the given advice whereas 43% did not. Ulcers present at the time of recruitment healed in 82% patients who followed the advice, but in only 50% patients who did not ($P < 0.0001$). A significantly larger proportion of patients who did not follow clinical advice developed new problems (26%) and required surgical procedures (14%) compared with those who followed the advice (5% and 3%, respectively) [44].

A National Foot Care Project

This project was developed to improve education and training of professionals offering diabetic care. The Step-by-Step project was implemented in India with generous funding from the World Diabetes Foundation (WDF) and academic support from the International Diabetes Federation (IDF), International Working Group on the Diabetic Foot (IWGDF), and the Diabetic Foot Society of India. A measured impact of the project was the development of 100 foot care clinics ("minimum model") in India [45].

Diabetic Foot Care: The State of Play in India

In India, organized diabetic foot-screening programs are very few. Podiatric services are available in major centers. There is a lack of multi-disciplinary team approach. Proper diabetic shoes and orthotics are not readily available while socio-economic factors encourage barefoot walking, inappropriate footwear utilization, and an overall lack of awareness to the seriousness of diabetic foot problems. This unawareness is shared among both doctors and patients and subsequently referrals to specialty centers are late — causing even further concerns. In India, 70% of the population lives in rural areas and 40% reside in one-room tenements. Improper foot offloading and inadequate sanitation due to a lack of facilities and awareness are commonalities. Very few people in India have health insurance while majority of patients with diabetic foot problems have to pay out of pocket for the cost of medical care, which hinders most from seeking prompt treatment.

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