The role of nontuberculous mycobacteria in cutaneous infections of diabetic patients: a literature review

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Background: Diabetes is an important metabolic disease with myriad manifestations and complications, affecting many people. Cutaneous infections impact numerous diabetic patients. Among different bacterial infections in diabetic patients, the infections caused by mycobacteria other than *Mycobacterium tuberculosis* (MOTT) eventuate in complications owing to the paucity of accurate detection methods.

Methods: The articles reporting nontuberculous mycobacteria (NTM) in cutaneous infections of diabetic patients, published until the end of 2017 were assessed in the present research.

Results: The organisms reported from cutaneous infections of diabetic patients are *Mycobacterium chelonae*, *Mycobacterium abscessus*, *Mycobacterium immunogenum*, *Mycobacterium kansasii* and *Mycobacterium fortuitum*.

Conclusion: NTM infection, along with prolonged disease cycle, decelerates the healing process in diabetic patients. Considering NTM during infection diagnosis, along with other possible opportunistic bacteria, conduces to accelerating the treatment process. In most cases, clarithromycin and erythromycin have been reported as effective alternatives for the treatment of diabetic patients.

Keywords: nontuberculous mycobacteria, diabetics, infection, cutaneous infections

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INTRODUCTION

Diabetes, a metabolic disease characterized by defective glucose metabolism in the body, is the most common endocrine disorder [1]. Since 2010, it has affected 285 million people around the world [2] and its increasing prevalence rate is because of today's lifestyles [3]. Diabetes is of two important types: Type I, also known as Insulin Dependent Diabetes Mellitus (IDDM), is caused by a series of genetic, environmental, and immunological factors. When insulin-producing cells are destroyed, the signs and symptoms of the disease appear. A series of genetic and environmental factors result in type II diabetes which is essentially characterized by resistance to insulin. Complications arise with the progression of the disease.

One of the complications associated with diabetes is the cutaneous complications. Both acute metabolic and chronic disorders impact diabetic patient's skin [4]. At least one in three diabetic people develop cutaneous manifestations in the course of the disease [4-6]. Cutaneous symptoms are observed following the development of diabetes or the signs may appear after several years [4,7,8].

It has been reported that the hyperglycemia of structural and regulatory proteins, induced by non-enzymatic glycation plays a critical role in pathogenesis of diabetic complications [1]. Excess supply of glucose leads to a non-enzymatic chemical

reaction between the amino acids of proteins and the carbonyl group of glucose, which is called Maillard reaction [4]. Insulin affects the proliferation, differentiation and migration of keratinocytes, so diabetic patients suffer from an altered function of these cells, which, in turn, eventuates in an insufficient function of the epidermal barrier and delayed healing [4]. There still exists controversy about the effect of diabetes on stratum corneum hydration. Superficial skin pH has a major role in cutaneous layer with its abnormally high values suitable for bacterial colonization as it is, more often than not, observed in chronic lesions. Additionally, in stratum corneum abnormal hydration, enhanced sebaceous gland activity and skin alternated elasticity are seen in diabetics [4,9]. Destruction of the cutaneous layer in diabetic patients augments susceptibility to bacterial infections. Also vasculopathy and neuropathy resulting from diabetes, lead to increased vulnerability to infections.

Among cutaneous infections such as candidiasis, dermatophitosis, and bacterial infections, the third is more common and more severe in diabetic patients. High glucose concentration converts the skin to an appropriate environment for saprophytic organisms [10]. Diabetic foot syndrome is reported in 15 to 25% of diabetic patients [11]. Toe web space infection causes inflammation and fissure, paving a way for the entrance of bacteria, resulting in diabetic foot infection [3]. Diabetic foot infection has various levels of deterioration and the probability of amputation has increased, particularly in developing countries (proportionate to the severity of the infection) [12]. In order to apply the optimal treatment against such infections, it is indispensable to perform accurate microbial identification. The organisms identified in diabetic lesions are *Staphylococcus aureus* [13,14] (specially in nasal carriages [15]), *Streptococcus agalactiae*, *Corynebacterium* spp., *Enterococcus* spp., *Proteus mirabilis, Escherichia coli*, *Peptostreptococcus* spp., *Bacteroides fragilis*, *Morganella morganii*, *Serratia marcescens*, *Klebsiella pneumoniae*, *Enterobacter aerogenes, Prevotella melaninogenica*, *Prevotella bivia*, *Fusobacterium* spp. [16], *pseudomonas aeruginosa* [17] and some non-tuberculous mycobacteria (NTM).

NTM include mycobacteria except for *M. tuberculosis* complex. ''Mycobacteria other than *M. tuberculosis* (MOTT) [18]" and "nontuberculous mycobacteria" are two collective terms employed for these organisms. The term "atypical mycobacteria" originates from a misconception that these bacteria, given their environmental distribution, are abnormal strains of *M. tuberculosis* [19]. The infections of these opportunistic human pathogens are more widespread in developed countries, in comparisons with developing and underdeveloped countries [20]. There is no evidence for person-to-person transmission. The increase in NTM infections is due to resistance to antimicrobials, increasing incidence of immuno-compromised hosts, human population aging, and failure in the detection of mycobacterial infection outbreaks [20].

Growth rate and pigment production in various temperatures are the most important phenotypic features of NTM. Nitrate reduction, catalase and urease activity, Tween 80 hydrolysis and arylsulfatase are among other important properties. NTM are comprised of two major groups; rapidly growing mycobacteria (RGM) and slowly growing mycobacteria (SGM). The latter group itself is divided into photochromogens, scotochromogens and non-photochromogens (non-pigmented) [21,22]. Generally, NTM grow in temperatures ranging from 25 to 45°C and may have dry, yellow, orange or creamy colonies which are easily emulsifiable [21,22].

Compared with molecular methods, biochemical tests are more time-consuming and less sensitive [23]. SGM and RGM are further differentiated by 16SrRNA gene analysis as a molecular method. Other molecular detection methods are PCR restriction enzyme analysis (PRA) for 65-kDa heat shock protein (*hsp65*) gene or RNA polymerase β-subunit (*rpoB*) gene [24-26]. To amplify a 441 base pair (bp) fragment of *hsp65* gene, Tb11 (5´-ACCAACGATGGTGTGTCCAT-3´) and Tb12 (5´-CTTGTCGAACCGCATACCCT-3´) were reported as forward and reverse primers, respectively [18].

NTM have relative resistance to a wide range of antimicrobials due to hydrophobic cell walls curbing the activities of many hydrophilic drugs and adaptation through continuous exposure to drugs [19]. Other examples of NTM pathogenicity factors are the prevention of acidification of phagolysosomes and the inhibition of fusing of phagosomes and lysosomes, resistance to the inhibitory effect of serum, delay in tumor necrosis factor (TNF) release in the host, receptors for macrophages and over expression of *cmaI* gene

which products (cyclopropane mycolic acid) are resistant to hydrogen peroxide [19]. The main objective of the present research was to investigate the role of NTM in cutaneous infections of diabetic patients, which, to the best of our knowledge, only a few studies have focused their attention on.

MATERIAL AND METHODS

A comprehensive literature search was conducted through the use of the electronic database including PubMed, Web of Science or Scopus for all articles published up to the end of 2017, on the NTM isolated in cutaneous infections of diabetic patients. It was beyond the scope of this study to examine the accuracy of isolation methods. The search was limited to English language.

RESULTS

It can be clearly implied from Table 1 that the isolated cases of diabetic cutaneous infections, include organisms such as *M. chelonae*, *M. abscessus*, *M. immunogenum, M. kansasii* and *M. fortuitum*. Infections occur at the site of insulin injection and a major etiologic factor for acquiring these infections, in addition to underlying diseases or the condition of the body, is the lack of perfect sanitation principles.

DISCUSSION

The present study aimed at assessing the role of NTM in the cutaneous infections of diabetic patients, indicating the necessity to consider these mycobacteria in the diagnostic procedures of medical laboratories. *M. chelonae, M. abscessus* and *M. immunogenum* are members of the *M. chelonae – M.abscessus* group (MCAG). These organisms are rapidly growing mycobacteria which belong to group IV of Runyon's classification. *M. abscessus*, in comparisons to other MCAG members, is more resistant to antibiotics [22]. *M. chelonae*, primarily isolated from a tortoise whose Latin name is *cheloei*, is widespread in the environment and its colonies are visible on growing media within a week [22]. *M. fortuitum*, whose name comes from 'fortuitous', meaning 'accidental' or 'casual' [26], belongs to RGMs with a worldwide distribution (tap water sources, dirt and sewage) and can play the role of an opportunistic human pathogen [27]. The first isolation was carried out in 1905 from infected frogs by Kuster [27]. *M. fortuitum* causes infections with various clinical manifestations, especially in immunosuppressed patients. It plays an important role in lung diseases, local cutaneous diseases, osteomyelitis, joint infections, ocular diseases and surgical site infections. Mortality due to infection is rare but morbidity is often related to the infection site [28]. Firstly identified by Buhler and Pollack in 1953, *M. kansasii*, which was primarily called yellow bacillus, is a photochromogenic member of the slowly growing mycobacteria, it has five genotypes, all of which are human pathogens [22]. The Clinical and Laboratory Standards Institute (CLSI) presented the criteria for the assessment of antimicrobial susceptibility of NTM. and defined the minimum concentration of antimicrobial agent which inhibits the organism, the Minimum Inhibitory Concentration (MIC), as one of the most important factors in antimicrobial susceptibility testing (ATS) of NTM [29]. In ATS process and its ultimate interpretation, mistakes such as contamination, inadequate growth, transferring mixed microbial load, and wrong results have to be precluded. Although some other factors associated with the sampling and the patient (unexpected fever, immunologic state and etc.) should be considered [29]. Methods of ATS are broth microdilution as the gold standard method for ATS of NTM and agar disk diffusion, a limitation of which is the difficulty in the interpretation of inhibition zone. Suitable turbidity of microbial suspension is a very important factor in this method which has not been standardized by CLSI and is employed merely as an ancillary method along with the broth microdilution. *E* test, previously known as Epsilometer test, is done after plates such as agar disk diffusion are inoculated [29,30]. Based on its type and clinical isolates, there are different ways of treating NTM. It is to be noted that macrolides such as, erythromycin and clarithromycin have been frequently used for the treatment of NTM.

CONCLUSION

Due to the special physiological conditions of diabetic patients, they are vulnerable to NTM infections. Given the resistance of NTM infections to the usual anti-tuberculosis treatments, NTM is

Table 1. Isolated cases of diabetic cutaneous infections caused by non-tuberculous mycobacteria

	Organisms	Country	Year of report	Isolation site	Underlying disease	Age (years old)/Sex	Identification method	Treatment	Reference number
1	M. *Chelonae*	Bristol, U. K	2003	right thigh injection abscesses	diabetes	43/woman	reference laboratory	clarithromycin and ciprofloxacin	31
2	M. *Chelonae*	Odisha, India	2013	axilla and inguinal regions	diabetes with Hidradenitis Suppurativa	28/man	phenotypic	clarithromycin, tobramycin and mupirocin	32
3	M. *chelonae*	Uttar Pradesh, India	2012	insulin injection on thighs and abdomen	type II diabetes	63/man	phenotypic	clarithromycin, linezolid	33
4	M. *chelonae*	Zaragoza, Spain	2012	fistula orifice on her right foot heel	history of type I diabetes	76/woman	phenotypic	imipenem, clarithromycin and levofloxacin	34
5	M. *chelonae* var *abscessus*	London, U. K	1980	right thigh	diabetes	24/woman	reference laboratory	erythromycin and co-trimoxazole	35
6	M. *abscessus*	Australia	2009	lesions on left anterior thigh	diabetes	48/woman	reference laboratory	clarithromycin and kanamycin	36
7	M. *chelonae*	Glasgow, Scotland	1987	lesions on both thighs	diabetes	18/woman	reference laboratory	susceptible to clofazimine, erythromycin and rifampicin	37
8	M. *abscessus*	Singapore	2009	abdomen	type II diabetes	59/woman	culture	clindamycin, metronidazole and ceftriaxone	38
9	M. *immunogenum*	Canada	2013	insulin injection on her right thigh	type I diabetes	47/woman	phenotypic and genotypic	susceptible to tigecycline and clarithromycin	39
10	M. *fortuitum*	Spain	2014	abdomen	type I diabetes	29/woman	-	ciprofloxacin and clarithromycin	40
11	M. *fortuitum*	Spain	2014	deep dermal abscesses	type I diabetes	34/woman	INNO LiPA MYCOBACTERIYA v_2 assay	doxycycline with ciprofloxacin	40
12	M. *kansasii*	France	2001	lesion on thighs	type I diabetes	84/woman	culture	clarithromycin	41
13	non-tuberculous mycobacteria	Singapore	2015	abdomen	type II diabetes	59/man	microscopic observation	ciprofloxacin and clarithromycin	42
14	non-tuberculous mycobacteria	Spain	2004	insulin injection site on abdomen	type II diabetes	59/woman	microscopic observation	clarithromycin	43

to be considered in routine diagnostic methods of medical laboratories. An early treatment will result in faster improvement, hence the significant of the evaluation of antibiotic susceptibility of these bacteria.

Conflict of Interest: None declared.

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