Overrepresentation of Diabetes in Soft Tissue Nontuberculous Mycobacterial Infections

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Abstract. Diabetes predisposes patients to bacterial infections. Although diabetes confers susceptibility to tuberculosis, the association between nontuberculous mycobacterial (NTM) infections and diabetes remains unknown. A retrospective chart analysis of patients in northern Australia during a 20-year period with soft tissue NTM infections revealed that patients with diabetes were three times overrepresented in comparison to the general population (odds ratio = 3.13). There was a statistically significant association between NTM infections and diabetes in this patient cohort ($P = 0.0082$).

There are over 150 nontuberculous mycobacterial (NTM) species which are capable of causing disease in humans.¹ Although tuberculosis (TB) is the most prevalent mycobacterial infection, epidemiological evidence indicates that there is an increasing incidence of pulmonary and soft tissue NTM infections.^{2,3} The risk factors contributing to pulmonary infections are complicated and often involve patients with severe underlying parenchymal lung disease. Hence, studies on this subset of patients are often confounded by a number of variables.^{2,3} In comparison, the risk factors contributing to soft tissue mycobacterial infections remain poorly characterized. Subsequently, in Australia, the highest rates of soft tissue NTM infections have been reported in northern Queensland where the current study was conducted.²

Diabetic patients have a higher risk of developing active TB, in addition to other intracellular bacterial infections such as listeriosis and melioidosis; however, the risk of acquiring NTM infections remains undefined.^{4,5} Diabetes is a multifactorial metabolic condition with a complex etiopathology. Exposure to chronic hyperglycemic conditions can induce oxidative stress, inflammatory changes, and immune dysfunction, thus contributing to the complicated pathologies that can arise from poorly controlled glycemia.⁶ Dysfunction in diabetes has been identified at all levels of the immune system through in vitro and in vivo studies. This can culminate in an increased occurrence of infectious diseases in patients with diabetes, along with a poorer prognosis.^{5,7} The increased susceptibility to bacterial pathogens in diabetes represents an important complication given the growing combined burden of communicable and noncommunicable conditions.^{4,5}

This study involved a retrospective chart review of patients with culture-positive soft tissue NTM infections presenting to the Townsville Hospital Human Research Ethics Committee (No. QTHS/HREC/43). In total, 44 patients were identified between 1995 and 2014. The criteria for diabetes was a fasting blood glucose above 6.5 mmol/L, glycosylated hemoglobin greater than 6.5%, or impaired oral glucose tolerance test (> 11.1 mmol at 2 hours after glucose administration), as per American Diabetes Association guidelines.⁸ The χ^2 test with Yates correction was used to assess whether a significant association existed between diabetes and TB and clinical outcomes.

In the current study, individuals with diabetes ($N = 6$; 13.3%) were three times (odds ratio = 3.13) overrepresented compared with the general population, and there was a significant association between diabetes and soft tissue NTM infections ($P = 0.0082$). The majority of patients with comorbid disease had type 2 diabetes ($N = 5$; 83.3%), and all diabetic patients were recorded as having poor glycemic control. All patients with soft tissue NTM infections were nonindigenous, and there were only two patients in the cohort born overseas (Table 1).

This study has shown that patients with diabetes may be more susceptible to soft tissue NTM infections, and is the first study to investigate this possible comorbidity. There was a higher prevalence of diabetes recorded in patients with soft tissue NTM infections in comparison to the general population as per the Australian Diabetes Map (13.3% versus 4.6%).⁹ This is congruent to findings from clinically based studies of the TB–diabetes comorbidity.¹⁰ The authors acknowledge that this study and its results do not prove causality given the smaller sample size. However, these figures demonstrate the need for further research in this area. NTM infections are challenging to treat, requiring long-term antibiotic therapy, and are also often overlooked as a potential source of infection. Clinicians must be aware of those populations that are more at risk of atypical infections for testing purposes, and in turn, to ensure appropriate antibiotic cover thus reducing the misuse of medications (Table 2).

Of the available data on NTM infections, a retrospective report by Uslan and others¹¹ found 16.7% of patients with soft tissue *Mycobacterium fortuitum* and 26.7% of patients with *Mycobacterium abscessus* or *Mycobacterium chelonae* had comorbid diabetes. An Australian study also recently reported an increased rate of edematous *Mycobacterium ulcerans* lesions in patients with comorbid diabetes.¹² In comparison, *M. ulcerans* ($N = 7$; 15.9%) was the second leading NTM species after *M. fortuitum* ($N = 15$; 34.1%), and one patient infected with *M. ulcerans* had comorbid diabetes in northern Australia. However, further studies are required to extend on these results (Table 3).

In the current study, comorbid diabetes exceeded all forms of immunosuppression, a leading contributor to the surge in infectious diseases.¹ As expected, in patients with soft tissue NTM infections, comorbid diabetes was surpassed only by tobacco use, a well-known risk factor associated with TB and other mycobacterial infections.^{2,3} Diabetic patients were equally likely to be of rural origin, and there was no significant difference between exposure/infection sources for diabetic or nondiabetic patients.

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TABLE 1
Demographical and microbiological characteristics of nontuberculous mycobacterial infections

Demography		Mycobacterial species % (no.)		Diabetic status % (no.)	
Patient no.	44	<i>Mycobacterium fortuitum</i>	34.1 (15)	Diabetic	
Mean age	43.0	<i>Mycobacterium ulcerans</i>	15.9 (7)	Type 2	11.4 (5)
Male:female	1.9:1.0	<i>Mycobacterium abscessus</i>	11.4 (5)	Type 1	2.3 (1)
Indigenous	0	Other	38.6 (17)	Gestational	0 (0)
Overseas born	2				

TABLE 2
Treatment and outcome of patients with nontuberculous mycobacterial infections

Infection site % (no.)		Treatment type % (no.)		Outcome of infection % (no.)	
Upper limb	18.2	Antibiotics	20.5 (9)	Treated	52.3 (23)
Lower limb	45.5	Surgery	4.5 (2)	Reactivation	25.0 (11)
Trunk	9.0	Both	70.5 (31)	Unknown	22.7 (10)
Other	27.3	Other	6.8 (3)		

TABLE 3
Comparison of nondiabetic and diabetic patients with nontuberculous mycobacterial infections

Risk	Nondiabetic (no.)	Diabetic (no.)
Diabetes	0	6
Chemotherapy	1	
Marijuana use	2	
Tobacco use	8	1
Alcohol	4	
CKD		1
Immunosuppression	2	
No known trauma	20	1
Trauma/s		
Surgical	5	
Soil	5	
Water		1
Metal	3	2
Past wound	3	2
Insect bite	3	
Location		
Outside state	1	
Urban	21	4
Rural	13	2
Unknown	2	
Diagnosis method		
Culture	27	5
PCR	3	1
Culture + PCR	2	
Histopathology	4	
Unknown	1	
Reason(s) for culture		
Failure treatment	13	4
Failure surgery	6	1
Misdiagnosis	2	
Biopsy ± excision	6	
FNAP or drainage	4	
Cellulitis/sepsis	1	1
Failure to heal	4	

PCR = polymerase chain reaction; CKD = chronic kidney disease; FNAP = fine needle aspirate.

The majority of the diabetes pandemic occurs in resource-poor regions where TB and environmental NTM infections are both highly endemic and where diagnostic facilities are rudimentary.^{3,13–15} Populations with impaired innate and adaptive immune responses on exposure to microorganisms are known to have the highest risk of acquiring active TB, as is the case in patients with diabetes.⁷ To our knowledge, previous studies had not addressed the possible comorbidity between diabetes and susceptibility to NTM infections. Diabetes was three times overrepresented in the study population and was a leading risk factor associated with soft tissue NTM infections. However, what is not clear is whether the high susceptibility in patients observed by us is a result of 1) diabetes and the wider metabolic syndrome, 2) complications associated with these disease states, or 3) a combination of both. A prospective study design with assessment of glucose intolerance and metabolic abnormalities at the time of diagnosis for NTM infections could provide adequate data to validate these assumptions.

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REFERENCES

- Orme IM, Ordway DJ, 2014. Host response to non-tuberculous mycobacterial infections of current clinical importance. *Infect Immun* 82: 3516–3522.
- Jackson E, Stewart A, Maguire EJ, Norton RE, 2007. Mycobacterial soft tissue infections in north Queensland. *ANZ J Surg* 77: 368–370.
- Hoefsloot W, van Ingen J, Andrejak C, Angeby K, Bauriaud R, Bemer P, Beylis N, Boeree MJ, Cacho J, Chihota V, Chimara E, Churchyard G, Cias R, Daza R, Daley CL, Dekhuijzen PN, Domingo D, Drobniewski F, Esteban J, Fauville-Dufaux M, Folkvardsen DB, Gibbons N, Gómez-Mampaso E, Gonzalez R, Hoffmann H, Hsueh PR, Indra A, Jagielski T, Jamieson F, Jankovic M, Jong E, Keane J, Koh WJ, Lange B, Leao S, Macedo R, Mannsaker T, Marras TK, Maugein J, Milburn HJ, Mlinkó T, Morcillo N, Morimoto K, Papaventsis D, Palenque E, Paez-Peña M, Piersimoni C, Polanová M, Rastogi N, Richter E, Ruiz-Serrano MJ, Silva A, da Silva MP, Simsek H, van Soolingen D, Szabó N, Thomson R, Tórtola Fernandez T, Tortoli E, Totten SE, Tyrrell G, Vasankari T, Villar M, Walkiewicz R, Winthrop KL, Wagner D, Group Nontuberculous Mycobacteria Network European Trials, 2013. The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: an NTM-NET collaborative study. *Eur Respir J* 42: 1604–1613.
- Hodgson KA, Morris JL, Feterl ML, Govan BL, Ketheesan N, 2011. Altered macrophage function is associated with severe *Burkholderia pseudomallei* infection in a murine model of type 2 diabetes. *Microbes Infect* 13: 1177–1184.
- Viswanathan V, Vigneswari A, Selvan K, Satyavani K, Rajeswari R, Kapur A, 2014. Effect of diabetes on treatment outcome of smear-positive pulmonary tuberculosis: a report from south India. *J Diabetes Complications* 28: 162–165.
- Baker RG, Hayden MS, Ghosh S, 2011. NF-kappaB, inflammation, and metabolic disease. *Cell Metab* 13: 11–22.
- Bridson T, Matthiesson A, Owens L, Govan B, Norton R, Ketheesan N, 2015. Diabetes: a contributor to tuberculosis in tropical Australia. *Am J Trop Med Hyg* 93: 547–548.
- American Diabetes Association, 2010. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 33 (Suppl 1): S62–S69.
- National Diabetes Service Scheme (NDSS), Diabetes Australia, Australian Government, 2015. *Australian Diabetes Map*. Available at: <http://www.diabetesmap.com.au/#/>. Accessed March 2016.
- Restrepo BI, Fisher-Hoch SP, Pino PA, Salinas A, Rahbar MH, Mora F, Cortes-Penfield N, McCormick JB, 2008. Tuberculosis in poorly controlled type 2 diabetes: altered cytokine expression in peripheral white blood cells. *Clin Infect Dis* 47: 634–641.
- Uslan DZ, Kowalski TJ, Wengenack NL, Virk A, Wilson JW, 2006. Skin and soft tissue infections due to rapidly growing mycobacteria: comparison of clinical features, treatment, and susceptibility. *Arch Dermatol* 142: 1287–1292.
- O'Brien DP, Friedman ND, McDonald A, Callan P, Hughes A, Athan E, 2014. Clinical features and risk factors of oedematous *Mycobacterium ulcerans* lesions in an Australian population: beware cellulitis in an endemic area. *PLoS Negl Trop Dis* 8: e2612.
- Falkingham JO, 1996. Epidemiology of infection by nontuberculous mycobacteria. *Clin Microbiol Rev* 9: 177–215.
- Weiss CH, Glassroth J, 2012. Pulmonary disease caused by nontuberculous mycobacteria. *Expert Rev Respir Med* 6: 597–613.
- Hur YG, Crampin AC, Chisambo C, Kanyika J, Houben R, Ndhlovu R, Mzembe T, Lalor MK, Saul J, Branson K, Stanley C, Ngwira B, French N, Ottenhoff TH, Dockrell HM, Gorak-Stolinska P, 2014. Identification of immunological biomarkers which may differentiate latent tuberculosis from exposure to environmental nontuberculous mycobacteria in children. *Clin Vaccine Immunol* 21: 133–142.