Letter to the Editor

How does metformin act as a host-directed agent in tuberculosis associated with diabetes mellitus?

Wing-Wai Yew[1], Denise P. Chan[1], Kwok-Chiu Chang[2], Ying Zhang[3]

[1]Stanley Ho Centre for Emerging Infectious Diseases, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China; [2]Tuberculosis and Chest Service, Centre for Health Protection, Department of Health, Hong Kong, China; [3]Department of Molecular Microbiology and Immunology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

Correspondence to: Dr. Denise P. Chan. Stanley Ho Centre for Emerging Infectious Diseases, The Chinese University of Hong Kong, 2/F, Postgraduate Education Centre, Prince of Wales Hospital, Hong Kong, China. Email: denisechan@cuhk.edu.hk.

Submitted Oct 18, 2019. Accepted for publication Jan 06, 2019.
doi: 10.21037/jtd.2020.01.30
View this article at: http://dx.doi.org/10.21037/jtd.2020.01.30

In a recent study based on informative data from the National Health and Nutrition Examination Survey of the United States of America, the use of metformin and statins was found to reduce the prevalence of latent infection due to *Mycobacterium tuberculosis* (*Mtb*) in subjects with diabetes mellitus (1). Furthermore, in an important study in Asia involving newly diagnosed diabetic patients without impairment of renal function, metformin use was independently associated with a lower risk of incident tuberculosis (TB) (2). In another useful study from the same Asian locality, the dose-dependent protective effect of metformin against the development of active TB, that appeared to wane with advancing age, was also demonstrated (3). A systematic review including a larger number of observational studies revealed a reduction of the risk of active TB disease but not latent TB infection associated with metformin use (4). The underlying mechanisms for these apparently beneficial effects of metformin in clinically modulating TB risk in global populations are likely complex and are not yet fully understood at present. It is imperative to better delineate these mechanisms through further research. We succinctly analyse the findings of two key studies (5,6), and briefly review other conceptual evidence to supplement the discussed implications of the results of these two pertinent studies. In doing so, we also hope to suggest research directions to explore the way forward in optimising the potential role of metformin as a host-directed therapeutic in TB.

A pioneer study has suggested an important contributory role of adenosine monophosphate-activated kinase signalling with increased production of mitochondrial reactive oxygen species (ROS) in macrophages, regarding the putative therapy effects of metformin against TB (5). ROS can kill intracellular *Mtb* directly by damaging DNA, protein and lipids or indirectly through oxidation of the pool of nucleotides by exploiting the Fenton reaction and tricarboxylic acid cycle (7).

In a follow-up study conducted by a similar group of investigators, peripheral blood mononuclear cells, $CD14^+$ monocytes or M1/M2 macrophages from healthy subjects, with or without metformin administration, were assessed under various experimental conditions, including stimulation with *Mtb* lysate. Summarising the results of this important latter study, metformin has shown an array of beneficial effects on the cellular metabolism, immune function and gene transcription in the innate host responses to *Mtb* (6). Specifically, there was significant downregulation of the genes associated with oxidative phosphorylation, mammalian target of rapamycin (mTOR) signalling and type 1 interferon response pathways, alongside upregulation of genes involved in phagocytosis and ROS production.

In the follow-up study, there was also a modification of the peripheral monocyte landscape shifting from classical to nonclassical cells, and a lowered production of some cytokines, especially those with putative proinflammatory activities, such as tumor necrosis factor alpha. Overall, metformin appeared to have modulated the host inflammatory response (6), quite in keeping

with the amelioration of lung pathology and reduction of chronic inflammation in the *Mtb* infected mice treated with metformin in the earlier study (5). However, in this follow-up study, metformin use only increased the *ex vivo* mycobactericidal activity of peripheral blood mononuclear cells in some but not all individuals (6), thus such findings are not fully consistent with the much better observed metformin-induced killing of tubercle bacilli inside human macrophages in the initial pioneer experiment (5). It is biologically plausible that this disparity in observed mycobacterial lethality might depend on the balance between the levels of ROS and salvaging antioxidants (7).

Interestingly, in the afore-mentioned follow-up study (6), mTOR downregulation/inhibition suggests autophagy induction. Autophagy plays a positive role in modulating latent TB infection with cumulative insights being uncovered in recent years, including, for example, the mechanistic contribution of heat shock protein 16.3 that might help to maintain long-term viability of dormant *Mtb* within macrophages through hampering the function of phagolysosomes (8). In an observational (clinical) study, autophagy was shown to improve with adjunctive metformin use to standard antituberculosis therapy in diabetic patients with TB (9). Furthermore, autophagy can possibly control both the pathogen burden and the host inflammatory response (10).

Importantly, in the follow-up study (6), the downregulation of genes involved in oxidative phosphorylation might also allude to the possible modulation of oxidative stress as part of the underlying mechanisms of action of metformin, in addition to perhaps its role in direct immune activation as suggested in the earlier study (5). Oxidative stress is likely associated with mitochondrial dysfunction resulting in disturbance of cellular metabolism and energy status. Metformin was indeed found to regulate cellular metabolism and improve mitochondrial functionality in the follow-up study (6). As there is also accumulating evidence regarding the close link between oxidative stress and inflammatory process (11), the favourable effect of modulating oxidative stress by metformin, as alluded, is consistent with its observed anti-inflammatory activity regarding the host responses to *Mtb* in both studies (5,6). In addition, growing basis also supports oxidative stress to be the converging point of various conditions such as nutrient deprivation and infection that enlist sustained autophagy through intracellular signal transducing, with AMPK conspicuously involved. It has also been discovered that p62 protein might activate the antioxidant transcription factor, nuclear factor erythroid 2-related factor 2, with Kelch-like erythroid cell-derived protein with CNC homology-associated protein 1 controlling its degradation. The accumulated knowledge helps in understanding the crosstalk between autophagy and oxidative stress (12). Indeed, in the clinical study alluded earlier (9), the elevation of the level of superoxide dismutase, an important antioxidant, occurred concomitantly with the increase in the level of microtubule-associated protein 1 light chain 3, a useful marker of autophagy activity.

Oxidative stress and immune dysfunction, inherent to the pathophysiology of diabetes mellitus and old age (11,13), possibly interact to increase the risks of latent infection due to *Mtb* and the development of active TB in these two important conditions comorbid to this globally prevalent infectious disease. One conceivable hypothesis, simplistically represented, is the increased propensity for formation of metabolically dormant bacillary persisters in the face of oxidative stress leading to latent TB infection that subsequently reactivates into active TB disease with progressive immune dysfunction of the diabetic host, especially in the face of ageing (13,14). Interactive cross talk between oxidative stress and immune function/response also probably exists. In the laboratory, there is now evidence that oxidative stress can induce the formation of *Mtb* persisters *in vitro* (15). Reduction of oxidative stress associated with metformin use has been well shown in a number of non-TB conditions and diseases through preclinical and clinical studies (16). More research is apparently warranted to delineate the role of metformin in ameliorating oxidative stress, or perhaps more broadly disturbance in redox homeostasis, as a contributory mechanism underlying the beneficial effects of metformin in host-directed therapy against TB. If such mechanism is unequivocally confirmed by further research, it might be possible to additionally explore the combined use of metformin and other antioxidants such as vitamin C, with likely similar action mechanisms, to optimise the efficacy and tolerability of metformin in managing TB (17).

To conclude, while improved understanding of the underlying mechanism(s) of metformin as a host-directed therapeutic in TB associated with diabetes mellitus has been achieved, further research especially regarding the roles of autophagy induction and amelioration of oxidative stress is likely warranted.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: Dr. Wing Wai Yew was consultant to Otsuka Pharmaceutical Company until July 2016. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Magee MJ, Salindri AD, Kornfeld H, et al. Reduced prevalence of latent tuberculosis infection in diabetes patients using metformin and statins. Eur Respir J 2019;53:1801695.
2. Lee MC, Chiang CY, Lee CH, et al. Metformin use is associated with a lower risk of tuberculosis among newly diagnosed diabetes mellitus patients with normal renal function: a nationwide cohort study with validated diagnostic criteria. PLoS One 2018;13:e0205807.
3. Lin SY, Tu HP, Lu PL, et al. Metformin is associated with a lower risk of active tuberculosis in patients with type 2 diabetes. Respirology 2018;23:1063-73.
4. Yu X, Li L, Xia L, et al. Impact of metformin on the risk and treatment outcomes of tuberculosis in diabetics: a systematic review. BMC Infect Dis 2019;19:859.
5. Singhal A, Jie L, Kumar P, et al. Metformin as adjunct antituberculosis therapy. Sci Transl Med 2014;6:263ra159.
6. Lachmandas E, Eckold C, Böhme J, et al. Metformin alters human host responses to Mycobacterium tuberculosis in healthy subjects. J Infect Dis 2019;220:139-50.
7. Shastri MD, Shukla SD, Chong WC, et al. Role of oxidative stress in the pathology and management of human tuberculosis. Oxid Med Cell Longev 2018;2018:7695364.
8. Zhang C, Yang L, Zhao N, et al. Insights into macrophage autophagy in latent tuberculosis infection: role of heat shock protein 16.3. DNA Cell Biol 2018;37:442-8.
9. Novita BD, Ali M, Pranoto A, et al. Metformin induced autophagy in diabetes mellitus tuberculosis co-infection patients: a case study. Indian J Tuberc 2019;66:64-9.
10. Matsuzawa-Ishimoto Y, Hwang S, Cadwell K. Autophagy and inflammation. Annu Rev Immunol 2018;36:73-101.
11. Halim M, Halim A. The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes). Diabetes Metab Syndr 2019;13:1165-72.
12. Filomenai G, De Zio D, Cecconi F. Oxidative stress and autophagy: the clash between damage and metabolic needs. Cell Death Differ 2015;22:377-88.
13. Yew WW, Yoshiyama T, Leung CC, et al. Epidemiological, clinical and mechanistic perspectives of tuberculosis in older people. Respirology 2018;23:567-75.
14. Yew WW, Leung CC, Zhang Y. Oxidative stress and TB outcomes in patients with diabetes mellitus? J Antimicrob Chemother 2017;72:1552-5.
15. Vijay S, Hai HT, Thu DDA, et al. Ultrastructural analysis of cell envelope and accumulation of lipid inclusions in clinical Mycobacterium tuberculosis isolates from sputum, oxidative stress and iron deficiency. Front Microbiol 2018;8:2681.
16. Yew WW, Chang KC, Chan DP, et al. Metformin as a host-directed therapeutic in tuberculosis: is there a promise? Tuberculosis (Edinb) 2019;115:76-80.
17. Yew WW, Chang KC, Chan DP, et al. Can vitamin C help in managing tuberculosis associated with diabetes mellitus? Respirology 2019;24:819-20.

Cite this article as: Yew WW, Chan DP, Chang KC, Zhang Y. How does metformin act as a host-directed agent in tuberculosis associated with diabetes mellitus? J Thorac Dis 2020;12(3):1124-1126. doi: 10.21037/jtd.2020.01.30