Catalysing future research on the under-recognised burden of post-tuberculosis pulmonary hypertension

There are now over 150 million TB survivors globally, yet the post-infectious sequelae related to this ancient disease remain woefully understudied. Over the past decade, however, there has been renewed interest in establishing the burden of post-TB lung disease (PTLD), characterising the diverse clinical phenotypes of PTLD, and quantifying the long-term morbidity and mortality attributable to the disease.[1] Recent estimates suggest a reduction of more than 15 disability-adjusted life-years among TB survivors in World Health Organization high-burden countries.[2] Moreover, our limited understanding of the immunopathological basis of distinct PTLD phenotypes (such as granulomas, cavitation, interstitial fibrosis, bronchiectasis, pleural fibrosis) has been highlighted as a key limiting factor to developing screening and diagnostic strategies for the disease, or indeed to contemplating potential therapeutic interventions.[3] While most chronic lung disease phenotypes are discernible by plain chest radiography or lung function testing, pulmonary hypertension after TB (PTLD-PH) is likely to be grossly underestimated owing to the limited availability of transthoracic echocardiography in primary care settings, where the vast majority of TB survivors receive care. In African settings, a history of TB is found in up to 27% of people with pulmonary hypertension (PH), and in up to half of all people with HIV who are diagnosed with PH.[4] It was recently found that between 9% and 16% of non-healthcare-seeking TB survivors had evidence of elevated pulmonary arterial systolic pressures, the vast majority of whom were pauci-symptomatic and had spirometric abnormalities indistinguishable from those in TB survivors without PH.[5] These findings raise the concern that pulmonary vascular involvement in PTLD may extend beyond PH, arising from extensive parenchymal destruction (i.e. group 3), but there is very limited characterisation of PTLD-PH beyond transthoracic echocardiography. The potential of a direct vasculopathic effect from an episode of TB is especially concerning, given that excess cardiovascular deaths account for a substantial proportion of the residual lifetime morbidity and mortality risk experienced by TB survivors (~5 times higher than the general population).

In this issue of *AJTCCM*, Payne *et al.*[6] provide a glimpse into the mechanistic abyss by exploring the potential role of mitochondrial dysfunction and oxidative stress in the pathogenesis of PTLD-PH.[6] Leveraging a parent cohort (the Pulmonary Artery Pressures in Pulmonary Tuberculosis Study II – PuPPeT II), the authors evaluated serum levels of key mitochondrial and antioxidant biomarkers in a cohort of survivors who had been successfully treated for TB at least 1 year previously. In light of the relatively little that is currently known about the pathogenesis of PTLD-PH, we can frame the results of this exploratory work as hypothesis-generating rather than as an attempt to map complex pathways or prove causation. A key discovery was a profound, generalised depletion in antioxidant capacity: serum levels of mitochondrial regulator metallothionein-1, catalase activity, and superoxide dismutase activity were magnitudes lower (up to 270-fold) than established normal ranges. Interestingly, these dramatically reduced antioxidant markers did not correlate with echocardiographic estimates of pulmonary artery systolic pressure or left ventricular filling pressure, nor were they influenced by the number of previous TB episodes. Furthermore, a key proxy marker of lipid peroxidation (thiobarbituric acid reactive substances (TBARS)) remained within normal limits, and hypoxia-inducible factor-1-alpha was completely undetectable, suggesting an unexpected absence of active hypoxia. Taken together, these findings suggest that a severe, persistent post-TB antioxidant-depleted state remains long after microbiological cure, presenting a novel potential contributor to the long-term sequelae of PTLD.

Like many early exploratory biomarker studies, detecting key biomarkers and assessing the directionality of effects can be difficult, reflecting the complexity of discerning direct causation, intermediate effects, and compensatory changes. The profound depletion of antioxidant enzymes, alongside normal TBARS levels and the lack of a direct correlation with PTLD-PH severity, raises intriguing questions about how oxidative stress manifests in these patients. These unexpected findings should not be viewed as failures, but as an incitement to pursue even more granular biomarkers, high-dimensional omics technologies, and integrative analytical approaches to fully illuminate the complex immunopathobiological mechanisms driving a lifetime of suffering, rather than a full recovery, following a discrete infectious TB event. Future work may benefit from a stronger set of counterfactuals to help delineate unique pathological pathways of PTLD-PH relative to other causes of PH, including: (*i*) people with idiopathic pulmonary arterial hypertension who have never had TB; (*ii*) people with group 3 PH without prior TB; and (*iii*) people with TB who recover without evidence of PTLD or PH. Ideally, the underlying pathological events should be paired with right heart catheterisation to delineate the precise anatomical location of the damage within the pulmonary vascular circulation and to understand their impact on cardiopulmonary haemodynamics. Given the potential scale of the PTLD-PH burden, the decades of neglected research and care must be swiftly replaced by cutting-edge science and an accelerated path to therapeutic interventions.[7]

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