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Diabetes and Tuberculosis: When Scylla Joins Charybdis

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Abstract: *Tuberculosis has been always considered a major health concern especially for low income countries. People with diabetes have shown increased prevalence of undiagnosed tuberculosis when compared to that of the general population.Research also indicates that those affected with infectious diseases are more likely to develop diabetes. There is enough evidence that demonstrates that people with tuberculosis and diabetes suffer the worse sequelae of both diseases. In these modern times, people with TB should not die, especially with the availability of modern pharmacological therapies and supervised regimens. Unfortunately, premature mortality attributable to both of these chronic diseases remains high. While there is a strong genetic predisposition, the recent rise in the incidence of diabetes suggests that genes alone are necessary but not sufficient to account for the mechanisms involved in diabetes disease onset. Therefore, environmental factors likely play a significant role, but the nature of these putative factors and their influence on the pathogenesis of diabetes is not yet known. Viruses, gut bacteria, nutritional deficiencies and chemicals have all been proposed as environmental catalysts for the development of diabetes. Of these, the intestinal flora (microbiome) is emerging as a critical factor in diabetes pathogenesis. Changes in the microbiome may also affect the immune response against infection. Here we explore how two major public health problems converge.*

Keywords: *Tuberculosis, diabetes mellitus, microbiome, Vitamin D*

1. INTRODUCTION

In Greek mythology, Scylla and Charybdiswere mythical sea monsters noted by Homer, who lived on opposite ends of the Strait of Messina. The idiomatic expression "Being between Scylla and Charybdis" means "having to choose between two evils"; but what if you cannot chose, and the presence of one calls for the other. This seems to happen for Diabetes mellitus (DBM) and Tuberculosis (TB), two diseases that seem to make things worse for one another. The insidious epidemic of obesity and diabetes is rising at an alarming pace that no one could predict, and the interactions of these two conditions are of particular concern.

We here briefly explore recent knowledge on clinical and biological aspects linking these two diseases.

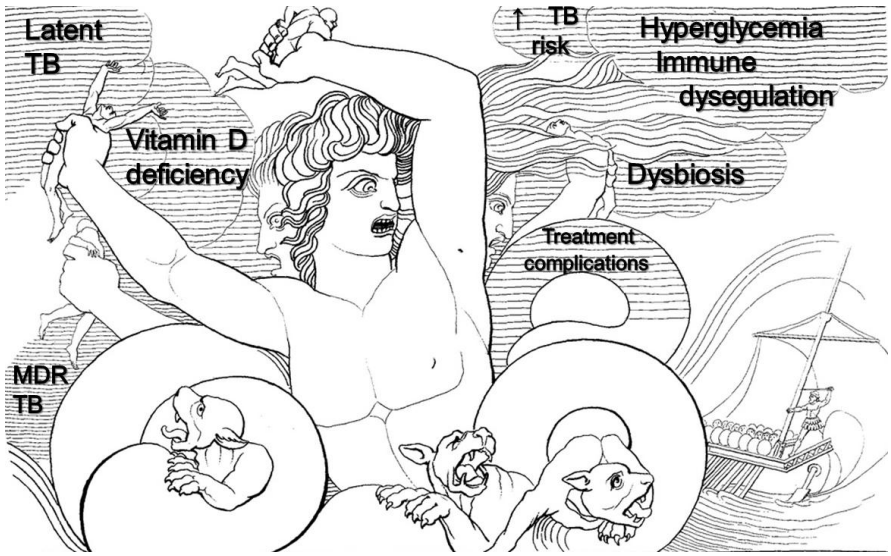

Figure1. *Image depicting Scylla and Charybdis, the two "monsters" from ancient Greek mythology*

In an analogy, two ominous public health problems converge when tuberculosis and diabetes are present. Diabetes impacts the natural history of TB due to the dysfunctional innate and adaptive immunity that occurs in this disease. Diabetes not only increases the risk of contracting tuberculosis, but it can also modify TB symptoms, radiographic findings, treatment, final outcomes and prognosis. It is important for clinicians and investigators to further explore the link between these two devastating diseases.

2. TUBERCULOSIS AND DIABETES: TWO MAJOR PUBLIC HEALTH PROBLEMS

TB affects around 9.4 million people and kills more than 1.3 million per year in the world [1][2]. TB has been always considered a major health concern especially for low income countries. In developing parts of the world the incidence of diabetes is also rapidly increasing [3]. Type 1 DBM is an autoimmune disease that affects millions worldwide [4]. Type 2 DBM is a global problem, which is expected to increase progressively in years to come, making it a major public health issue worldwide , and has been defined as an obesity-driven global disease [5]. People affected by DBM are at higher risk of acquiring other comorbidities due to the immune depressed state that the illness present on the face of metabolic derangements of DBM that can predispose the individual for associated illness. It is well know that individuals with good control of their DBM are less likely to acquire infections, including TB. In developing parts of the world the incidence of DBM is also rapidly increasing. Up to 80% of cases of DBM are occurring in the developing world, in low and in middle income countries, and the individuals with DBM type 1 and type 2 are at higher risk of contracting TB. In 2013 investigators from the World Diabetes Foundation revealed that DBM increases the risk for active TB 2 to 3 fold, with the highest risk being in the individuals with the poorer glucose control. [6]. The increased risk for TB in DBM patients may contribute to the resurgence of TB, negatively affecting its control. As pointed out by the Pan American Health Organization, DBM contributes considerably to the burden of TBs in the Americas Region, accounting for 15.4% of the total number of TB cases [7]. Among factors that affect TB control, DBM is a key challenge. The complex relationship between TB and DBM has been recently reviewed, analyzing past trends, the present burden and future global projections. Odone et al. utilized a mathematical model to estimate the potential effect of DBM and TB through the year 2035. [8]. The rising rates of obesity and DBM, particularly in developing countries which also harbor high prevalence of TB, poses concern that DBM may become a threat to global TB control.

3. PULMONARY TB IN THE DIABETIC PATIENT

Diabetes impacts the natural history of TB due to the dysfunctional innate and adaptive immunity in the diabetic patient [9]. A major challenge that has been overlooked is the growing prevalence of DBM worldwide poses a risk for the control of tuberculosis, since DBM leads to a greater risk of developing TB. Recent studies have demonstrated that the increase prevalence of DBM in some countries went a la par with an increased number of people who acquired TB. What this association suggests is that there may be links between these two devastating diseases, and this deserves further investigation. [10]. Other studies have looked into the association of DBM and TB both in underdeveloped and developed countries [11]. These studies concluded that people with DBM have 2.5 times higher risk of acquiring TB [9, 12]. Diabetes not only affects the increased risk of *Mycobacterium tuberculosis* (Mtb) infection and TB development, but it also modifies its clinical presentation and treatment outcomes. Variations in disease presentation are likely the result of interaction or additive effects between the contribution of diabetes to immune dysfunction and a variety of additional host factors that also affect immunity (e.g., smoking) [9]. Chronic hyperglycemia is associated with dysfunctional immunity to Mtb and also affects the microvasculature by reducing lung tissue perfusion for optimal immune surveillance in diabetic patients [13]. It has been shown that appropriate TB treatment in patients with diabetes leads to better glycemic control[14]. Besides being a risk factor for TB, diabetic patients with TB may be more likely to develop drug-resistant TB [15-17]. Diabetes can modify TB symptoms, radiographic findings, treatment, final outcomes and prognosis [18, 19]. Diabetic complications such as renal insufficiency complicates the treatment of TB as some anti-TB drugs are cleared by the kidney [20]. Higher body mass index (BMI) in diabetic patients may have a negative effect on the pharmacokinetics of drugs and on TB treatment [18]. A recent study has shown DBM to be a risk factor for TB relapse [21]. Lastly, diabetic TB patients have a higher mortality in comparison with TB or DBM only [22], making DBM a risk factor for death in TB patients.

4. Microbiome changes in DBM. Its implications in TB pathogenesis and therapy

The development of high throughput sequencing technologies has enabled the study of the role of gut microbiota in the development and progression of DBM[23]. The results at times show discrepancy in the bacterial composition between cases and controls, however, epidemiological and animal studies have shown a decrease in gut microbiota diversity associated with DBM[23-25]. Age, ethnicity, the immune system and diet are main regulators of the intestinal microbiota. A high-fat diet may induce dysbiosis, which can result in a low-grade inflammatory state, obesity and other metabolic disorders [5]. Besides genetic susceptibility, which plays an important role in its etiology, there are strong indications that gut microbiota dysbiosis plays an important role in Type 1 DBM development [23]. Data from animal models and humans also suggest that obesity and type 2 DBM are associated with a profound dysbiosis[24, 26]. Gut dysbiosis and diet-induced gut permeability could be environmental factors in the development of obesity before the development of DBM[27]. Furthermore, a recent study demonstrated that gut dysbiosis and possible blood bacterial translocation in patients with type 2 DBM is an important modifier of disease [28]. The gut microbiota is essential for the host immune system[29]. Innate immune adaptor molecule MyD88, essential for Toll-like receptor signaling, as well as NOD receptor and testosterone levels have been linked with alterations in the gut and implicated in DBM development [23]. How alterations of the microbiome (dysbiosis) might contribute to an unhealthy immune response that sets up the individual for the development ofMtbinfection and metabolic complications, is still unknown.

5. Vitamin D supplementation on TB therapy for DBM patients

The role of vitamin D in TB has been well known, with reduced serum levels of this vitamin associated with active TB [30]. The active form of vitamin D leads to the induction of antimicrobial peptide cathelicidin LL-37 thus increasing the intracellular killing of mycobacteria [31, 32]. Vitamin D deficiency has been identified as a co-risk factor required to activate molecular signaling, including impaired insulin signaling and secretion, that ends with Type 2 DBM and associated diseases [33]. In fact severe vitamin D deficiency appears to be present in patients with TB and DBM [34]. Dietary changes, such as prebiotics and vitamin D supplementation, may be useful not only in managing pre-diabetes and type 2 DBM[33], but as treatment for TB in these patients. Two recent reports have shown that vitamin D supplementation promotes macrophages anti-mycobacterial activity in diabetic patients with low vitamin D receptor expression [35, 36]. It also increases LL-37 levels and T helper-associated response in patients with DBM and TB [32, 37]. Vitamin D has recently been evaluated as an adjuvant for TB treatment. Although a reduction in positive sputum after vitamin D supplementation was observed, it was not statistically significant [38]. Still, future studies may help in the evaluation of the value of vitamin D supplementation in patients with both morbidities.This could have enormous public health implications, as population-wide supplementation measures may help to prevent both diseases globally.

An important challenge comes at the moment of treatment when these two diseases are associated. Diabetes not only increases the risk of an individual to develop TB, but it will also make it more difficult to treat[39]. Baker et al found that people with DBM are more likely to fail TB treatment and they are more likely to die compared to those individuals without the disease. [40, 41]

6. Conclusions

It is important for clinicians and investigators to further explore the link between these two devastating diseases. One of the strategies could be to establish appropriate screening protocols for the assessment of tuberculosis in patients with DBM, and vice versa, to screening patients with TB for the presence of risk factors for DBM and DBM itself. These approaches must increase the rate of diagnosis for both diseases with aims of early detection and prevention of TB and DBM related complications, especially if associated. This is important because in people with uncontrolled DBM, management of TB could lead to better control of the DBM and less complications. Further studies to clearly elucidate the role of the microbiome and vitamin D in these two diseases could lead not only to newer and promising treatment options for TB in diabetic patients, but help in the progression and development of DBM itself.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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