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Mini-Review

Tuberculosis and diabetes: did the chicken or the egg come first? An immunologic point of view

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ABSTRACT

The causes of type 1 diabetes are unknown, although the role of genetics is likely, since we can observe an association with some histocompatibility antigens, like HLA-DR3,-DR4 and DQ2; in particular, among genetic factors some haplotypes like HLA-DRB 09 seems to be linked to higher frequency of pulmonary tuberculosis associated with diabetes, while HLA-DQB has a "protective" role against the association. Besides, the higher frequency of both diseases in migrant populations stress the importance of the "environment" as a trigger. The link between these two diseases could be justified by immunological impairments that characterize diabetes, like lower CD4/CD8 ratio, impaired number and function of blood cells like granulocytes and monocytes. Literature shows that patients with both the diseases in response to protein purified derivative (PPD) have an overexpression of some inflammatory cytokines such as IL-2, IL-8, TNF-alpha and IFN-gamma (key Th1 cytokine, critical for tuberculosis control and usually up-regulated by *M. tuberculosis*). Among several hypothesis suggested to explain this paradoxical finding, the most plausible is focused on a modification in protein functions due to an increase in glycation products, which is responsible for a massive suppression of downstream signal transduction of Th1 lymphocytes and innate immunity cytokines, essential against *Mycobacterium tuberculosis*. One other possibility justifies the increased level in production of Th1 cytokines that is constantly observed in diabetic patients, with higher bacterial load in the lung in the early stage of tuberculosis, since, in fact, the increase in risk infection is a typical diabetic feature.

KEYWORDS: tuberculosis, diabetes, lymphocytes, genetics.

INTRODUCTION

Since the end of 19th century, the association between tuberculosis and diabetes is known: Apollinaire said that "…..At autopsy, every case of diabetes had tubercles in the lungs….". Several decades later , Root underlines that "…In the latter half of the 19th century the diabetic patient appeared doomed to die of pulmonary tubercolosis if he succeeded in avoiding death for diabetes." On the other hand, there is also the possibility that a transitory diabetes mellitus could appear in patients suffering from tuberculosis, maybe induced by chemotherapy or surgery [1].

Genetics

Nowadays, we know that the natural history of diabetes is unavoidably conditioned by genetic factors (familiarity, association with histocompatibility antigens like HLA-DR3, DR4 and DQ2): in support of this argument, Ruggiero *et al*. report that, comparing old,

"historical" (in other words diagnosed at least 20 years before) and recently diagnosed tuberculosis patients, observed in Southern Italy, no significant association between different HLA alleles and Tb in the second group was observed. On the contrary, among the old, "historical" Tb patients, there was a strong association with an increased frequency of the HLA-DR4 allele alone, and/or in the presence of the HLA-B14 allele [2]. Such a result is not easy to explain: we could speculate that HLA-DR4 allele could be linked to a less severity of disease, since these "historical" patients, suffering from Tb in pre-antibiotic era, survived only by pneumothorax treatment.

Zhao underlines that HLA-DRB 09 seems to be susceptible to pulmonary tuberculosis associated with diabetes: in fact, in such an haplotype, there is a higher frequency of both diseases, while HLA-DQB may be protective [3].

Besides genetic factors, also "environment" could represent a trigger, since both diseases are more frequent in migrant populations, suggesting the possible role of stress in the pathogenesis.

Immunology

Besides, it is well known that in diabetic patient a lot of immunological impairments are present:

- a lower CD4/CD8 ratio;
- an impaired chemotaxis, fagocytosis, and killing of granulocytes;
- a lower C3 opsonization;
- a reduction of number and function of blood monocytes.

An elegant paper by Restrepo *et al*. report that in poorly controlled type 2 diabetes, there is an altered cytokine expression in peripheral white blood cells, if exposed to PPD: in particular, IL-2, IL-8, TNF-alpha, and IFN-gamma seem to be overexpressed, mimicking what could happen *in vivo* during comorbidity Tb/diabetes [4].

IFN-gamma is a key Th1 cytokine usually up-regulated by *M. tuberculosis*, and hence its role is critical for tuberculosis control.

In Restrepo's study, patients with tuberculosis and diabetes show a significantly higher production of IFN-gamma in response to PPD versus tuberculosis patients without diabetes. This finding may appear not so easy to explain, even paradoxical, because patients with diabetes are, as we know, more susceptible to tuberculosis. A plausible hypothesis to explain such a result is that diabetic patients can show alterations in the downstream signal transduction of Th1 lymphocytes and innate immunity cytokines, owing to an increase in glycation products that can bind and modify protein functio. This mechanism could determine suppression of downstream responses, essential against *M. tuberculosis*, despite high levels of protective cytokines, which could be dysfunctional due to advanced glycation.

One other possibility is that diabetic patients may produce increased levels of Th1 cytokines owing to higher bacterial load in the early stage of tuberculosis, as observed in the mouse model of combined tuberculosis and diabetes [5, 6, 7].

Clinical aspects

Diabetes is one of the main causative factors of risk of infection, together with advanced age, smoking, obesity, and immunosuppression.

Moreover, lung could represent a preferential "habitat" for *Mycobacterium tuberculosis*, since diabetic patient shows a huge reduction of bronchial reactivity, of alveolo-capillary diffusion, elastic recoil, and ventilatory answer to hypoxemia.

Besides, the evidence of a strong association of DM and active TB disease is confirmed by the meta-analysis 'Diabetes Mellitus increase the risk of active tuberculosis: a sistematic review of 13 observational studies' by Jeon [8, 9, 10].

The study also found that the link between DM and TB in the study populations from Central America [9], Europe and Asia, was higher than those from North American studies.

Despite DM was positively associated with TB disease, the meta-analysis also showed a stronger link in those studies in which DM was diagnosed prior to TB, than those in which the timing of DM and TB diagnosis wasn't clarified [9-16].

A higher risk of association between these two diseases was seen among younger people, in areas with high burden of TB disease, and in non-North American populations. Stevenson *et al*. showed

that DM accounts for 80.5% of incident pulmonary TB among diabetes patients, and 14.8% of incident TB in the total population in India [17].

Another study conducted during 3 years in Bangalore, South India, reported that DM was an important risk factor for developing TB, with a prevalence rate of 22.2% in TB and 15.9% in non-TB subjects [18].

The importance of using a routine screening for DM among TB patients in areas with a high burden of TB is stressed by various retrospective analysis: one conducted in Saudi Arabia shows that the prevalence of DM in TB subjects is 27% [19]; another one from Taiwan reported 16.9% of DM among TB patients [20]. A prospective study conducted by Alisjahbana *et al.* in Indonesia reported a 14.6% prevalence of DM among patients with TB compared with 3.2% in general population [21].

CONCLUSIONS

In the light of a lot of Literature's data concerning a strong link between diabetes and tuberculosis, even if it is not so clear if the first disease could represent a risk factor for the second one, or the contrary, we can point out that in clinical practice it is mandatory to look for both: diabetes among Tb patients, and Tb among diabetes patients.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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