Hypothesis: Melatonin and its possible role in mediating the seasonal variability of tuberculosis

Sir,

Tuberculosis (TB) is a significant health problem worldwide, and is caused by *Mycobacterium tuberculosis*. Among the one-third of the world infected by *M. tuberculosis,*[1] almost 8 million new cases of TB occur annually, with 2 million deaths attributed to the disease each year. Only 10% of those individuals infected by *M. tuberculosis* go on to develop clinical disease. The seasonal peak of TB has been reported, in different countries, to be during the spring and summer seasons.[2] Although the exact mechanism underlying the fluctuation of tuberculosis in a particular time of the year is still not clear, several researchers have suggested that the environmental factors (temperature, humidity, and sunlight) as well as crowding and person-to-person contacts are important determinants of Mycobacterium survival and the affect pathogens' transmissibility.[3] This explanation applies to primary or reinfection TB but not to reactivation TB. To explain the seasonal trend of both reactivation and primary TB, it is usual to consider that the main cause of TB seasonality is intrinsic.[4] However, the questions related to seasonality of tuberculosis remain controversial. To date, no one has seriously proposed the possible relationship between the seasonality of melatonin and the possible influence on clinical manifestations of TB.

Melatonin is a hormone produced mainly by the pineal gland, and other organs such as retina, kidney and digestive tract have also been reported to be producers of this hormone. Recently, it was found that human peripheral blood mononuclear cells synthesize a biologically relevant amount of melatonin. The immunomodulatory properties of melatonin are well known; it acts on the immune system by regulating the cytokine production of immunocompetent cells. Experimental and clinical data show that melatonin plays a key role in stimulating the production of interferon-gamma (IFN-γ), natural killer (NK), interleukin-2 (IL-2), interleukin-6 (IL-6) and interleukin-12 (IL-12) and also has a stimulatory influence on the production and physiological actions of granulocytes and macrophages.[5] The seasonal changes in immune function observed in animals and humans are likely to be mediated by the changes in the duration of melatonin secretion[6] because the clinical manifestations of infection with *M. tuberculosis* reflect the balance between the bacillus and host immunity. This fact may, in part, account for the cyclic pattern of symptom expression shown by TB, which becomes more pronounced in spring and summer. Based on this knowledge, one can propose a hypothesis: that melatonin may play an important role in the seasonal variability of TB. The possible explanation of this idea, that the winter time is related to the secretory rhythm of melatonin, gives a better immune response against *M. tuberculosis* compared with spring and summer, obviously not preventing infection but allowing to control it in winter, whereas the infection later (spring and summer time) progresses to disease. A second theoretical advantage is that melatonin may play an efficient role in enhancing the immune system against *M. tuberculosis*, particularly in the spring and summer season, which may offer new preventive and therapeutic options for the management of TB patients and contacts, as well as the higher risk group such as HIV patients or immune compromised persons.

Melatonin has been administered in both physiological and pharmacological amounts to humans and animals, and there is widespread agreement that it is a nontoxic molecule and is inexpensive.[7] To evaluate this hypothesis, it is needed to investigate the influence of exogenous melatonin on the immune response against *M. tuberculosis* in winter and summer as well as to estimate the serum level of endogenous melatonin in TB cases compared with healthy controls in winter and summer. It is possible to evaluate the influence of exogenous melatonin *in vitro* with and without anti-TB on the clinical TB response. The efficacy of melatonin has been assessed as a therapeutic and protective agent in several diseases. However, there is only one report concerning the effect of melatonin on the viability of *M. tuberculosis*.[8] Because melatonin was ineffective in an *in vitro* clinical trial, it will be a good idea to test the hypothesis.

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