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Vitamin Deficiency and Tuberculosis: Need for Urgent Clinical Trial for Managment of Tuberculosis

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Abstract

The scenario of tuberculosis is getting complicated due to the emergence of multiple drug resistant and extensively drug resistant strains. The advent of BCG vaccination is understood to be a failure as far as primary prevention of the disease. In this context, there is a considerable current interest of development of host based chemotherapies for management of the disease. Since malnutrition is a recognized associate of tuberculosis from times immemorial the role of vitamin deficiency is reviewed keeping in view the molecular pathogenesis of the disease. Considering the recent evidences relevant to the subject, we have concluded that there is an urgent need for clinical trial of several vitamins for the management of tuberculosis.

Keywords: Tuberculosis; Vitamin; Malnutrition; Antioxidant; Neuropathy

Introduction

Tuberculosis is one of the deadliest bacterial killers affecting almost all corners of the globe. In-spite of the discovery of antitubercular antibiotics and an available vaccine (BCG vaccine) against *Mycobacterium tuberculosis* we are unable to tackle the occurrence of tuberculosis. Moreover the increasing prevalence of HIV-AIDS and diabetes mellitus is being proved to be providing predisposition to tuberculosis (Global tuberculosis control–surveillance, planning, financing [1-5]. As witnessed by the WHO, which has estimated that, in the year 2012, 8.6 million people have developed tuberculosis and 1.3 million have died of the disease, including 320000 deaths of HIV-TB co-infected people [6]. Long term multiple antibiotic therapy, which is associated with many adverse drug related events have diminished patient compliance with the anti-tubercular chemotherapy. This fact, in turn, has raised the new, deadlier MDR-TB and XDR-TB strains [7-9]. The whole scenario of current day tuberculosis is a matter of panic. It questions the effectiveness of anti-tubercular antibiotics, immunologic efficacy of century old BCG vaccine and all other medical advents present at the moment to combat tuberculosis.

Malnutrition has always been recognized to be a very important predisposing factor for all infectious diseases including tuberculosis [10-12]. Vitamin deficiency and malnutrition are the biggest challenges in the developing nations where the disease burden of tuberculosis is noticeably very high. Vitamins are bio-molecules that maintain body's physiology and boost the protective immune system. Vitamins are responsible for a spectrum of vital functions in the body due to their anti-oxidant, pro-oxidant, anti-inflammatory effects and metabolic functions [13-17]. The anti-oxidant system of the human body is largely contributed by anti-oxidant vitamins (vitamin-E, C, A). The anti-tubercular effects of vitamins are also being studied since the pre-streptomycin age, but till today systematic clinical trial of vitamin supplementation is lacking in the scenario of tuberculosis. It is in this context, we have reviewed the role of major vitamins in the background of tuberculosis.

Vitamin-A

Vitamin A metabolites are essential for normal growth and development. This boosts up both body's natural innate immunity as well as the adaptive immunity [18-23]. Retinoic acid, a vitamin-A metabolite has been shown to inhibit expression of toll like receptor-II (TLR-II) on the cellular surface and thus affect the TLR-II signalling pathway and prevents *Mycobacterium tuberculosis* and other gram positive bacteria cause human infections [20,24-31]. It also increases the phagocytic activity of human macrophages [32]. Importantly, a recent study has found that retinoic acid alone or with iron can reduce the transferring receptors up to a significant level in promonocytic cell line U937 [33]. This might lead to a restriction in the availability and accessibility of iron in the intracellular environment. Iron is essentially needed by Mycobacterium tuberculosis for almost all of its strategies for successful intracellular survival and pathogenecity in human hosts, including the activity of enzymes against oxidative burst, supply of oxygen to hypoxic atmosphere by mycobacterial truncated haemoglobins, arresting phagosome-lysosome fusion and acidification in an iron dependant manner, host cell cholesterol utilization etc [34-64]. Moreover, this retinoic acid (vitamin A) along with vitamin D_3 or with hepatic chenodeoxycholic acid can reduce the synthesis tryptophan aspartate coating protein (TACO) by down regulation of TACO gene expression at the transcriptional level [65,66]. TACO protein

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is believed to be very essential for the mycobacterial entry and successful intra-phagosomal survival in the macrophages as it inhibits the phagosome maturation i.e., the phagosome-lysosome fusion and acidification and thus contribute in the pathogenecity and virulence of *Mycobacterium tuberculosis* [67,68]. Vitamin A helps in the normal function of immune cells and also enhances the synthesis of iNOS and other essential cytokines with antitubercular activity [69-77]. Moreover, oral administration of retinoic acid can reduce mycobacterial growth *in vivo* and physiological and pharmacological doses of retinoic acid in pre and post infectious conditions show preventive and therapeutic effects respectively [74,78]. So, deficiency in dietary vitamin-A can hamper the activity of both innate and adaptive immunity while supplementation can boost the body's fight against Mycobacterium tuberculosis along with the administration of anti-tubercular drug regimens.

Vitamin-B

Though the direct association between tuberculosis and vitamin-B deficiency is not known, but vitamin-B supplementation is well recommended in order to avert several neurological complications in tuberculosis patients. Administration of pyrazinamide, isoniazid while treating tuberculosis commonly causes vitamin-B_6 deficiency in the body which in turn gives rise to different peripheral neuropathies [79,80]. It is also reported that vitamin-B_{12} deficiency is a cause of neuropathy in patients with ileal tuberculosis [81].

Vitamin-C

Vitamin-C is well known for its anti-oxidant and pro-oxidant actions [82-83].As an immunological maintenance measure vitamin-C can enhance the function of the immune system in different ways like T-lymphocyte proliferation etc. and thus strengthens the cell mediated immunity [84-88]. Both lower dietary intake and lower blood concentration of vitamin-C are considered to be associated with the higher incidence of tuberculosis [89,90]. In patients with active cavitary tuberculosis, the anti-oxidant vitamin-C level gets substantially decreased with an increase in lipid peroxides [91-93]. Vitamin-C can halt spreading of infections including tuberculosis. It also accelerates recovery from tuberculosis by healing decay cavity and turns sputum acid fast bacillus (AFB) negative [94]. Most interestingly in a recent study, vitamin-C has been shown to have an extraordinary capability of killing of drug susceptible, multi-drug resistant (MDR) and extensively drug resistant (XDR) *Mycobacterium tuberculosis*, which strongly suggest and support the incorporation of vitamin-C and iron (needed for its strong mycobactericidal action) supplementation along with the anti-tubercular antibiotic therapy [95]. Paradoxically, it is believed that the blind exogenous administration of antioxidants may augment the mycobacterial antioxidant system to protect itself in patient suffering from tuberculosis, but experimental supports are there which show that an adequate dietary supplementation of vitamin-C contributes protection against tuberculosis and lowers the incidents [94,96-98]. Adequate anti-oxidant vitamin supplementation along with standard anti-tubercular antibiotic regimen has been demonstrated to accelerate healing of tuberculosis [94].

Vitamin-D

Vitamin D is well known for its pivotal role in bone mineral density (BMD) and calcium homeostasis in the body [99]. Vitamin D deficiency and its association with tuberculosis is very well known from the pre-antibiotic era as in those days exposure to sunlight and vitamin D supplementation (cod liver oil) were the most reliable treatment choice for treating tuberculosis [100-101].

It is believed that vitamin-D deficiency is associated with increased infection of the upper respiratory tract [99]. Till date, a large number of studies have proven the association between vitamin D deficiency and the occurrence of tuberculosis [102-107]. Vitamin D receptors (VDR) are found to be present on different immune cell surfaces including T and B cells suggest that, they need vitamin-D for performing the cellular functions [99]. Vitamin D has been shown to increase the phagocytic activity of macrophages. Monocytes incubated with cholecalciferol (vitamin-D_3) metabolites have been shown to induce anti-tubercular activity [108]. Moreover, it enhances the production of the body's antimicrobial/antimycobacterial peptide LL-37, a member of the cathelicidin peptide family [109-111]. Vitamin-D also enhances the fusion of phagosome and lysosome, a very significant step towards the elimination of intra-phagosomal *Mycobacterium tuberculosis* from the human body [110,112]. Vitamin-D deficiency has been recognized as a major risk factor for tuberculosis as low serum vitamin-D found to be associated with the development of active tuberculosis. Hypovitaminosis D is also found as a common feature in HIV positive patients and maybe that's why the most common opportunistic infection in these people is tuberculosis [113,114]. Vitamin-D supplementation in this HIV-TB co-infected patient population has shown some amazing hope with sputum clearance and radiological improvement which in turn caused an appreciable reduction in mortality [115].

Vitamin-E

Several studies have reported substantial reduction of anti-oxidant vitamin-E in patients suffering from tuberculosis. Alpha tocopherol (vitamin-E) is as capable as ascorbic acid (Vitamin-C) in cavity healing in active cavitary tuberculosis and thus having an accelerating role in healing tuberculosis [94,116].

Vitamin-K

Vitamin-K has vital functions in the formation of coagulation factors by the liver. Hepatotoxic anti-tubercular drug (e.g.; Pyrazinamide, Isoniazid, Rifampicin) induced hepatotoxicity may hamper the blood coagulation physiology e.g., cerebral hemorrhage is reported due to vitamin-K deficiency in patients suffering from congenital tuberculosis [117].

Pre-infective routine dietary nutrition with essential vitamins and minerals has effective preventive capability against the occurrence of disease tuberculosis. Multivitamin

supplementation along with anti-tubercular antibiotic therapy is very much needful as it provides anti-tubercular capability to the body, accelerates healing of *Mycobacterium tuberculosis* caused cavity and ulcer, reduces anti-tubercular drug induced adverse effects and helps the body reclaiming normal physiological function of affected organs. Dietary vitamin supplementation as a measure of nutritional up gradation will definitely help in effective tuberculosis treatment and also low down the prevalence of tuberculosis especially in the countries with higher disease burden. However, blind supply of antioxidant vitamins may also be harmful. Therefore, we feel systematic clinical trials should be conducted focusing on the above area to construct a combination regime of vitamin supplementation that can combat tuberculosis.

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