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Mini Review

Malnutrition: A Potent Threat to Tuberculosis Affected Children

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Abstract

Tuberculosis is a lethal bacterial infection around the globe. Its severity is more potent in poor economic countries. Every year more than 10 million tuberculosis cases are reported, of which 11% are children. Socioeconomic factors such as malnourishment, poverty, unhygienic lifestyle, TB contact, HIV infection etc. worsen the situation further. From available research we can say that malnutrition is a predictor of this disease with worse outcomes both in adults and children. Malnourishment leads to reduced immune response to fight tuberculosis. thymic atrophy, reduced functions of APCs, shifting of Th1 response to Th2 type are thought to be related to malnourishment in children. Malnourished children are poor responder of vaccination and supplementation treatment against TB. Malnourishment among children of a TB endemic country is surely a main problem in eradicating TB. But there are more research needs on childhood TB emphasising on malnourishment.

Keywords: *Tuberculosis; Malnutrition; Child Health; Immune Response*

Abbreviations

TB: Tuberculosis; WHO: World Health Organization; HIV: Human Immunodeficiency Virus; HR: Hazard Ratio; APCs: Antigen-presenting Cells; Th; T Helper cell; IL-: Interleukin; TNF: Tumor Necrosis Factor; IFN: Interferon; BMI: Body Mass Index

Introduction

Mycobacterium tuberculosis, the causative agent of tuberculosis, is the most lethal infectious organism globally especially in a settings of restricted resources. In 2016, near about 10.4 million people were affected by tuberculosis and the number of deaths are 1.3 million people [1]. Among this new infection pool 11% children are affected every year [2]. In tuberculosis (TB) endemic countries malnutrition is highly prevalent in children and contributes to 2.2 million deaths in children less than 5 years of age worldwide [3]. Only 39% of child TB cases were reported that highlight under-diagnosis and under-reporting of TB in children [4]. Almost 815 million people majority living in low- and middle-income countries such as in sub-Saharan Africa and Southeast Asia which has high rates of tuberculosis [1,5], are suffered from malnourishment. There are many factors for e.g. poverty; overcrowding; limited resources; food insecurity; etc cumulatively deteriorate the situation for both malnutrition and poor regulation of tuberculosis. According to the World Health Organization (WHO), malnutrition is a significant risk factor for childhood tuberculosis [2] and they also estimated that the under-nutrition is an important factor that doubles the number of TB cases as human immunodeficiency virus (HIV) worldwide [1]. Targeting this malnutrition, it is feasible to reduce the mortality rate of tuberculosis by 95% by 2035 [6].

Nutritional status and tuberculosis

Considering the level of protein intake, it was observed that those who intake proteins < 50% of normal were more prone to tuberculosis infection. A 13.8% reduction (95% CI, 13.4% - 14.2%) in tuberculosis incidence per unit increase in BMI was reported in high-income countries [7]. An increased BMI may also reduce the chances of death during treatment for tuberculosis [8]. Little or low quality food

intake, metabolic dysfunction, poor absorption, fever, and anorexia are main reasons of weight loss in TB patients. Tuberculosis leads to altered metabolism and anabolic block. That is why dietary proteins are not used in anabolism but in energy production [9,10]. Several studies suggest that under-nutrition is related to tuberculosis mortality. Studies in African countries for e.g. in Ethiopia; South Africa; have expressed that low body weight at the start of the treatment due to under-nutrition or malnourishment is one of the reason for tuberculosis mortality [11,12].

Role of nutritional status on immune response against tuberculosis

Both innate and adaptive immunity together take part to fight against *M. tuberculosis* [13]. It is found that the malnourished children have impaired innate immunity due to less active antigen-presenting cells (APCs); neutrophils; and toll-like receptors (TLRs); as well as low levels of blood complement [14,15]. Breast milk is early stage of nutritional source in infants. Various important immune factors present in it help to develop mucosal immunity in children [14,16]. Based on facts, maternal nutrition is indispensable to provide protection and also to build a functional innate immunity in children.

Th1-type response is also critical against this intracellular bacterium [13]. Several studies have suggested that due to under-nutrition reduced size of thymus gland (maturation site of T lymphocytes); thymic atrophy in malnourished children results in higher infant mortality due to tuberculosis or other infections [17-19]. Protein deficiency and inadequate zinc intake leads to thymic malfunction [19,20]. Polyunsaturated fatty acids particularly the anti-inflammatory omega 3 (n-3) fatty acids in tuberculosis-infected individuals, decrease lymphocyte proliferation, is shown by an *in vivo* study [21]. Tuberculosis affected individuals who already have low protein diet are incapable to build sufficient Th1-type response along with reduced levels of IL-2, TNF-α, and IFN-γ [22]. Shifting of Th1-type response to Th2-type along with its respective cytokine profile in malnourished children may exacerbate the defence mechanism against *M. tuberculosis* [23]. Additionally, undernourished children accounted impaired T-cell activation when compared to the well-nourished controls [24]. Adults who have BMI < 18.5 suffering from tuberculosis, show low circulating levels of IFN-γ, TNF-α (Th1-type cytokines) and high circulating levels of IL-5, IL-13 (Th2-type cytokines) in comparison to individuals who have BMI > 18.5 [20].

Newborns vaccinated at birth with BCG showed that mild or moderate malnourishment in infants had reduced tuberculosis-associated cell-mediated immune responses [25]. The impact of under-nutrition on vaccine response is subjected to much more investigation. Various factors such as micronutrient deficiencies, malabsorption, which are results of under-nutrition make those suffered individuals poor responder to TB vaccines [26]. Therefore, the nutritional status of vaccine recipients should be an important criterion to develop an effective tuberculosis vaccine.

Probable solutions

To get the solution, we need to look forward and should emphasize for extensive research on this topic. Clinical trials have shown mixed results. It was suggested that nutritional supplementation of zinc may promote stronger cell-mediated immunity in malnourished children [27]. The role of macro- or micronutrient supplementation in children with active tuberculosis is not evident. However, there are numerous limitations in assessing supplementation trials [28,29]. Vitamin A supplementation in children may initiate shifting towards Th1 type responses which is crucial for defence against tuberculosis [30].

Discussion

It was reported that the 27% of the population in 22 High TB-endemic countries are suffering from malnutrition [31]. The spread and prognosis of TB is very much related to the socio-economic and nutritional status and malnutrition [32,33]. Globally, in low-income section of the society due to the limitation of income people suffer from malnutrition and couldn't afford proper health care services. Malnutrition increases the susceptibility to tuberculosis [34,35]. Additionally, other factors which include overcrowding, improper sani-

tizations, low economic-status along with co-morbidities such as human immunodeficiency virus (HIV), and diabetes mellitus (DM) etc act as induction for tuberculosis [36-38]. To eradicate TB the World Health Organization (WHO) has identified the need for an inclusive approach towards socio-economic determinants of TB [39]. To achieve this goal by the year 2030 sustainable development is the main thrust area in all countries which includes economic development and environmental sustainability [40].

As most of the drugs for tuberculosis are in tablet and capsule forms, tuberculosis treatment is becoming difficult for children except rifampicin. Extensive research on following issues such as to understand the TB load among malnourished children at different levels of care; identification of prognostic markers and improved diagnostics in children with acute malnutrition; risk factors for TB to children with acute malnutrition; are most inevitable to treat malnourishment related tuberculosis in children. Government of a tuberculosis-endemic country should make proper guidelines as well as they must encourage and provide financial support to patients for treatment.

Conclusion

In conclusion, malnourishment is undoubtedly responsible for childhood TB and which is the reflection of uncontrolled adult TB. The accurate diagnosis and identification of prognostic markers of TB is necessary for effective treatment and detection of contact cases of infected children suffering from malnourishment. Low socio-economic status, TB contacts, poor nutrition, low body weight etc. altogether initiate childhood TB. Therefore, extensive depth level of research is indispensable to find out optimal timing of initiation, safety and efficacy of TB medications in acutely malnourished children and needs proper monitoring for side effects.

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Conflicts of Interests

Authors declare that there is no conflict of interest.

Authors Contributions

PCG planned the idea for this mini-review article. KC and PCG both performed all the literature search and data analysis. KC finally drafted and critically revised the work.

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