Does vitamin A supplementation decrease the risk of progression of tuberculosis among household contacts?

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SUMMARY

This study by Aibana *et al*. was a nested case–control design within a cohort of household contacts of adult patients diagnosed with tuberculosis (TB) in Lima, Peru. The primary objective was to assess the association of vitamin A deficiency and progression to TB disease, and the interaction of vitamin D deficiency with this pathway. Previous studies had reported a similar association but its causality was not documented. In this study, a case was defined as an HIV-negative household contact who developed incident TB during the 1-year follow-up period of the study. Age- and sex-matched controls were selected from the cohort in the ratio 1:4. Blood samples were collected from the participants and stored at –80 °C, and were analysed at the end of the follow-up period to look for deficiencies of retinol, carotenoids and vitamin D by standard estimation methods. Matched case–control analysis, adjusted for confounders, was done using the conditional logistic regression model. The model was tested with stratification on the baseline status of TB infection and restriction to cases diagnosed at least 90 days after enrolment of the index case and microbiologically confirmed TB. The results showed that even though there was a difference between both the groups at baseline, favouring the control group with (i) respect to isoniazid therapy; (ii) history of TB infection; (iii) latent TB infection; and (iv) serum retinol levels, a significant association between vitamin A deficiency and conversion to TB disease remained even after adjustment for these factors. Biological gradient was also present, with higher odds of TB progression in the lowest quartile of serum retinol compared to the higher quartiles. Interaction between vitamin A deficiency and vitamin D deficiency was not statistically significant. Sensitivity analyses did not yield different results. Corroborative findings were documented in previous researches, albeit in different populations. It was concluded that vitamin A status strongly predicts the progression to TB disease in a dose-dependent manner.

COMMENT

Although the calculation of sample size was not mentioned in the article, as per our own calculations, using McNemar's formula in Stata v12.0 for matched case–control study, we found it to be adequate.

The authors have identified a few limitations of the study, notably misclassification of controls. However, they have not discussed lagged exposure bias in a nested case–control study. Vitamin A deficiency, even if not present at the start of the study when serum retinol levels were measured, can occur during the follow-up period or vice versa. This would incorrectly categorize the cases as unexposed in the matched analysis, leading to an underestimation of the odds ratio. The authors did not provide enough information regarding recruitment of controls to differentiate the nested case–control and case–cohort study designs, as both are dealt differently during analysis. Similarly, a 2×2 matched pair table is not provided.

Finally, we assess how this study fits with the Hill's criteria for causality:

1. *Strength of association.* Yes. Compared to household contacts of adult patients with TB who have not developed the disease in the 1-year follow-up period, the chances of finding vitamin A deficiency are 10 times more in those who developed TB.
2. *Consistency*. Yes. Sensitivity analysis shows that this association holds true in different strata. Moreover, this association is also shown in previously published studies.
3. *Specificity*. No. Many other exposure variables show an association with risk of progression to incident TB disease. Also, previous studies have assessed multiple factors that show a similar strength of association with progression to TB

disease. Hence, specificity cannot be concluded with certainty.
4. *Temporality*. Yes. What came first: vitamin A deficiency or TB disease? This is answered by the prospective study design which takes into account only the incident cases.
5. *Biological gradient*. Yes. It was shown that the odds ratio is higher for the lowest quartiles of vitamin A levels compared to the higher levels; this trend is shown to be statistically significant. Even if serum retinol is not low enough to classify vitamin A deficiency, a dose-dependent increase in the strength of association is seen with lower values of serum retinol.
6. *Biological plausibility*. Yes. Retinoic acid, the active form of vitamin A in the body, is a potential immune-modulator affecting both the adaptive and innate immune response. A deficiency can thus lead to increased survival and multiplication of TB bacilli in the body leading to progression of disease.
7. *Coherence*. Yes. It is known that risk of TB progression increases in immunocompromised states. Vitamin A deficiency leads to a similar immunocompromised state.
8. *Experiment*. No. This study is observational and no supplementation of vitamin A is done. However, the same is proposed by the authors and can be undertaken in future.
9. *Analogy*. Yes. As an analogy, diseases such as measles and other infections are more common in vitamin A deficient compared to vitamin A sufficient populations. Similar mechanisms might be at work in the case of *Mycobacterium tuberculosis* too.

Vitamin A deficiency has been previously shown to be associated with the risk of progression to TB disease, but the causality of this association is still being debated.

Thus, we observe that this study ticks most boxes in the Hill's criteria. Undertaking an experimental trial to confirm this hypothesis is ethically challenging and requires enormous resources. A stepped-wedge cluster randomized trial, or a similar study design, might be feasible and ethically sound to confirm the hypothesis.

Indian context

India contributes the largest share to the global burden of TB. In 2015, 2.8 million (28 lakh) cases and 0.48 million (4.8 lakh) deaths due to TB were reported in India.[1] Even though the prevalence of TB has decreased over the years, the burden of multidrug-resistant (MDR)-TB is on the rise.[2] Latent TB infection is estimated to be present in 40% of the Indian population,[3] and 10%–15% of latent infection is estimated to convert to full-fledged disease.[4] Currently, it costs India ₹13 500 to treat a patient of TB, and the cost for treating MDR-TB is much higher. Each rupee spent on preventing TB may give benefits of up to ₹70 to India.[5]

India is estimated to have the highest burden of vitamin A deficiency among Southeast Asian countries.[6] In children aged 1–5 years, the prevalence of vitamin A deficiency was 62% and Bitot's spot was 0.8% in 2006,[7] which is higher than the set cut-off of 0.5% above which vitamin A deficiency is said to be of public health concern. More recent studies from other countries show prevalence among adults ranging from 1.2%[8] to 7.8%.[9]

Considering the huge economic burden of TB in India, a possible intervention of vitamin A supplementation must be considered, at least among contacts of patients with TB, in view of the recent evidence of its protective effect. This might help accelerate the programme towards India's ambitious goal of elimination of TB by 2025. The programmatic cost of vitamin A supplementation, which was estimated at ₹3.20 per person per year in 1998,[10] came down to ₹0.99 in 2004.[11] A more recent estimate is not available.

Isoniazid chemoprophylaxis for asymptomatic children under 6 years (contacts) has been prescribed under the Revised National TB Control Programme.[12] Also, vitamin A supplementation for children under 5 years of age is part of the National Immunization Programme. Hence, there is a platform and an opportunity for the Government of India to introduce vitamin A supplementation to contacts of TB under the ambit of national health programmes.

Conflicts of interest. None declared

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