

COCHRANE CORNER

Nutritional supplements for people being treated for active tuberculosis: A technical summary

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Tuberculosis and nutrition are intrinsically linked in a complex relationship. Altered metabolism and loss of appetite associated with tuberculosis may result in undernutrition, which in turn may worsen the disease or delay recovery. We highlight an updated Cochrane review assessing the effects of oral nutritional supplements in people with active tuberculosis who are receiving antituberculosis drug therapy. The review authors conducted a comprehensive search (February 2016) for all randomised controlled trials comparing any oral nutritional supplement, given for at least 4 weeks, with no nutritional intervention, placebo or dietary advice only in people receiving antituberculosis treatment. Of the 35 trials ($N=8\ 283$ participants) included, seven assessed the provision of free food or high-energy supplements, six assessed multi-micronutrient supplementation, and 21 assessed single- or dual-micronutrient supplementation. There is currently insufficient evidence to indicate whether routinely providing free food or high-energy supplements improves antituberculosis treatment outcomes (i.e. reduced death and increased cure rates at 6 and 12 months), but it probably improves weight gain in some settings. Plasma levels of zinc, vitamin D, vitamin E and selenium probably improve with supplementation, but currently no reliable evidence demonstrates that routine supplementation with multi-, single or dual micronutrients above the recommended daily intake has clinical benefits (i.e. reduced death, increased cure rate at 6 and 12 months, improved nutritional status) in patients receiving antituberculosis treatment. In South Africa, most provinces implement a supplementation protocol based on nutritional assessment and classification of individuals rather than on disease diagnosis or treatment status.

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There is a complex relationship between tuberculosis and nutrition.^[1] The immunodeficiency caused by undernutrition increases the risk of acquiring tuberculosis.^[2] Alternatively, tuberculosis may cause undernutrition through increased metabolic demands and decreased appetite. The resulting nutritional deficiencies may worsen the disease or delay recovery by depressing immune function.^[3,4] A key guiding principle of the World Health Organization guidelines on nutritional care and support for patients with tuberculosis^[5] is that 'an adequate diet, containing all essential macro- and micronutrients, is necessary for the well-being and health of all people, including those with TB infection or TB disease'. However, owing to limited available evidence there is still no evidence-based nutritional guidance specific to adults and children who are being treated for active tuberculosis. We summarise the evidence from an updated Cochrane review assessing the effects of oral nutritional supplements on all-cause death and cure at 6 and 12 months in patients receiving treatment for active tuberculosis.^[1]

Methods

The review authors conducted a comprehensive search of eight databases up to February 2016, without language or date restrictions. All randomised controlled trials comparing any oral nutritional supplement, given for at least 4 weeks, with no nutritional intervention, placebo or dietary advice only to patients receiving

treatment for active tuberculosis were included. The review authors followed standard Cochrane methods for independent screening and eligibility assessment, data extraction, risk of bias assessment and data analysis. The quality of the evidence was assessed using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach.^[1]

Results

Of the 35 eligible trials ($N=8\ 283$ participants), four were conducted in children ($n=739$) and 11 specifically presented disaggregated outcome data for HIV-positive and HIV-negative participants. Most of the trials were conducted in Africa and Asia.

Macronutrient supplementation

Seven trials investigated the effect of providing free food or high-energy nutritional supplements. The trials were too small to reliably demonstrate or exclude clinically important benefits on mortality (risk ratio (RR) 0.34, 95% confidence interval (CI) 0.10 - 1.20; four trials, 567 participants, very low-quality evidence), cure (RR 0.91, 95% CI 0.59 - 1.41; one trial, 102 participants, very low-quality evidence), or treatment completion (data not pooled; two trials, 365 participants, very low-quality evidence). Providing free food or high-energy nutritional supplements probably produces modest weight gain during treatment for active tuberculosis, although this

was not consistent across all included trials (data not pooled; five trials, 883 participants, mean weight gain 0.78 - 2.6 kg, moderate-quality evidence). There is some evidence that quality of life may be improved, but the trials were too small to have much confidence in the result (data not pooled; two trials, 134 participants, low-quality evidence) (Table 1).^[1]

Multi-micronutrient supplementation

Six trials assessed multi-micronutrient supplementation in doses up to 10 times the recommended dietary allowance (RDA).^[6] Routine multi-micronutrient supplementation may have little or no effect on mortality in HIV-negative people with tuberculosis (RR 0.86, 95% CI 0.46 - 1.6; four trials, 1 219 participants, low-quality evidence), or HIV-positive people not taking antiretroviral therapy (RR 0.92, 95% CI 0.69 - 1.23; three trials, 1 429 participants, moderate-quality evidence). There is insufficient evidence to know whether multi-micronutrient supplementation improves cure (no trials), treatment completion (RR 0.99, 95% CI 0.95 - 1.04; one trial, 302 participants, very low-quality evidence), or the proportion of people who remain sputum-positive during the first 8 weeks of antituberculosis treatment (RR 0.92, 95% CI 0.63 - 1.35; two trials, 1 020 participants, very low-quality evidence). Furthermore, multi-micronutrient supplementation may have little or no effect on weight gain during treatment (data not pooled; five trials, 2 940 participants, low-quality evidence),

and no studies have assessed the effect on quality of life. The summary of findings for multi-micronutrient supplementation is available for the outcomes death, cure rate, treatment completion, remaining sputum-positive (4 weeks), weight gain and quality of life.^[1]

Single- or dual-micronutrient supplementation

Eighteen trials assessed single- or dual-micronutrient supplementation. Low vitamin A levels are common in tuberculosis, and plasma levels of vitamin A appear to increase following initiation of antituberculosis treatment regardless of supplementation. There is no evidence that vitamin A supplementation in doses up to three times the RDA has a beneficial effect on tuberculosis treatment outcomes (i.e. death (RR 0.97, 95% CI 0.84 - 1.12; eight trials, 3 308 participants), sputum smear- or culture-positive after 4 weeks (RR 0.70, 95% CI 0.33 - 1.48; one trial, 148 participants)) or nutritional recovery (body mass index: RR 0.3, 95% CI -0.44 - 1.04; one trial, 148 participants). In contrast, supplementation probably improves plasma levels of zinc, vitamin D, vitamin E and selenium, but this has not been shown to have clinically important benefits. Of note, despite multiple studies of vitamin D supplementation in different doses, statistically significant benefits on sputum conversion have not been demonstrated (number of participants who were sputum smear- or culture-positive after 4 weeks: RR 0.87, 95% CI 0.74 - 1.03; five trials, 929 participants).^[1]

Table 1. Summary of findings: Food provision (calorie supplementation as food or energy-dense supplements) compared with standard care (nutritional advice or no intervention) for adults and children with active tuberculosis*

Outcomes	Standard care	Increased calorie intake	Relative effect	Number of participants (trials)	Quality of the evidence (GRADE)
Death (at 6 months) (95% CI)	3 per 100	1 per 100 (0 - 4)	RR 0.34 (0.10 - 1.20)	567 (4 trials)	Very low ^{†§§}
Cured (at 6 months) (95% CI)	48 per 100	44 per 100 (28 - 68)	RR 0.91 (0.59 - 1.41)	102 (1 trial)	Very low ^{†§§}
Treatment completion (at 6 months) (95% CI)	79 per 100	85 per 100 (70 - 100)	Not pooled	365 (2 trials)	Very low ^{§ **}
Sputum negative (at 8 weeks) (95% CI)	76 per 100	82 per 100 (65 - 100)	RR 1.08 (0.86 - 1.37)	222 (3 trials)	Very low ^{§ **}
Mean weight gain (at 8 weeks) (95% CI)	-	-	MD 0.78 (-0.05 - 1.6)	883 (5 trials)	Moderate ^{†††§}
Quality of life (change in quality of life score), mean (SD)	At 6 weeks: 13.33 (24.76)	14.47 (25.43) 8.33 (22.49) (27.38)	Not pooled	134 (2 trials)	Low ^{§§§§}

CI = confidence interval; SD = standard deviation; RR = risk ratio; MD = mean difference; GRADE: Grading of Recommendations Assessment, Development and Evaluation. GRADE Working Group grades of evidence:

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

*This technical summary is an adapted version of a Cochrane Review Summary of Findings table previously published^[1] in the Cochrane Database of Systematic Reviews 2016, Issue 6, <https://doi.org/10.1002/14651858.CD006086.pub4> (see www.cochranelibrary.com for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

†Three trials reported some deaths during the 6 months of treatment (Jahnavi 2010; Jeremiah 2014; Sudarsanam 2010), and one reported that no deaths occurred (Martins 2009). The trials were conducted in Tanzania, Timor-Leste, and India in participants with signs of undernutrition. Martins 2009 gave a daily hot meal, Sudarsanam 2010 gave monthly ration packs, Jahnavi 2010 gave daily locally appropriate supplements, and Jeremiah 2014 gave high-energy multivitamin-enriched biscuits.

‡Downgraded by 1 for indirectness: trials are only available from limited settings. Food supplementation would plausibly have its biggest effect in highly food-insecure or emergency settings, which are not reflected in these trials.

§Downgraded by 2 for imprecision: the trials and meta-analysis are significantly underpowered to either detect or exclude an effect if it exists.

¶Data on successful cure at 6 months are only available from Sudarsanam 2010, which randomised tuberculosis patients in India to monthly ration packs or advice only.

||Two trials report on tuberculosis treatment completion at 6 months (Jahnavi 2010; Martins 2009). One trial was conducted in India and one in Timor-Leste in participants with signs of undernutrition. Both trials gave daily locally appropriate supplements.

**Downgraded by 1 for inconsistency. Jahnavi 2010 found a statistically significant benefit, while the larger trial, Martins 2009, did not.

††Five studies reported measures of weight gain but at different time points, which prevented meta-analysis. The relative effect was derived from three trials (Jeremiah 2014; Martins 2009 and Praygod 2011b) that provided change and/or actual mean weight data at 8 weeks.

‡‡Downgraded by 1 for inconsistency. Praygod 2011b included only HIV-positive patients, and although the trend was towards a benefit, this did not reach statistical significance. Jeremiah 2014 noted a greater increase in mean weight gain in the supplemented group compared with the non-supplemented group after 8 weeks; however, the difference was not appreciable (1.09 kg, *p*<0.6, authors' own figures). The three other trials all demonstrated clinically important benefits.

§§Downgraded by 1 for indirectness. Only two small trials, one from Singapore (Paton 2004) and one from India (Jahnavi 2010), report quality-of-life scores. The results cannot be generalised to other populations or settings with any certainty.

§§§Downgraded by 1 for imprecision. The presented data appear highly skewed and could not be pooled.

Conclusion

The review authors concluded that based on the current research they do not know whether routinely providing free food or energy supplements results in better antituberculosis treatment outcomes (decreased tuberculosis-related mortality, increased cure rate, increased tuberculosis treatment completion rate); however, limited evidence suggests that it probably improves weight gain in some settings. There is also no reliable evidence that routine supplementation with multi-micronutrients or specific individual micronutrients above recommended daily amounts has clinical benefits. Of note for future research, according to the review authors' calculations, none of the included trials or meta-analyses of trials were sufficiently powered to detect clinically important effects on the outcomes of interest.^[1]

This evidence in the South African context

Tuberculosis is the leading cause of underlying natural deaths in South Africa (SA), even through the proportions of natural deaths attributed to tuberculosis have declined over time (8.8% in 2013, 8.3% in 2014, 7.2% in 2015).^[7] The 2016 *Global Tuberculosis Report* estimated that SA had the sixth-greatest number of incident cases and third-greatest incidence in relation to population.^[8] The incidence of multidrug-resistant (MDR) and extensively drug-resistant tuberculosis is increasing, and SA is deemed at risk of having a MDR tuberculosis-dominated tuberculosis pandemic.^[9]

According to the 2015/2016 *District Health Barometer*,^[10] the incidence of tuberculosis in SA has decreased over the past 5 years, with the most notable decline in KwaZulu-Natal Province. The Eastern Cape, KwaZulu-Natal and Western Cape have the highest incidence of tuberculosis, while Mpumalanga, Gauteng and Limpopo provinces rank the lowest. Districts with the highest tuberculosis incidence were Sarah Baartman (Eastern Cape), Pixley ka Seme (Northern Cape) and Nelson Mandela Bay (Eastern Cape).^[10]

While the national guiding document on nutritional supplementation is being finalised, most provinces implement a supplementation protocol based on the nutritional assessment and nutritional classification of individuals rather than on disease diagnosis or treatment status. Nutritional supplementation is discontinued when nutritional status goals are met. Macronutrient supplementation practices often depend on budget and human resource availability, and mostly involve providing undernourished individuals with varying quantities (range 2 - 7 kg per month) and combinations of enriched maize porridge, enriched energy drinks and *mageu* (lactic acid-fermented maize-based drink). Eligibility criteria for nutritional supplementation differ between provinces and according to age, mostly referring to a body mass index <18.5 kg/m² in adults.

Two recent studies in adult tuberculosis patients in Delft in the Western Cape^[11] and Standerton in Mpumalanga (J Wessels, 'Nutritional status of patients with tuberculosis and TB/HIV co-infection at Standerton TB Specialised Hospital, Mpumalanga, unpublished data) show that newly admitted patients with active tuberculosis are undernourished (body mass index <18.5 kg/m²). Considering the findings of these studies and the Cochrane review, the current national nutritional supplementation practices, which focus on addressing undernutrition in general rather than disease-specific nutritional requirements, would appear to be appropriate. One exception may be pregnant women with active tuberculosis. In pregnant women, tuberculosis is associated with high mortality rates and poor treatment outcomes, and as such these women may require additional nutritional support.

In SA, the burden of tuberculosis disproportionately affects people who are chronically impoverished, hungry and malnourished, who have an increased risk not only of developing tuberculosis but also of poor tuberculosis treatment outcomes.^[12,13] National data show that almost a third (28.3%) of all adults are at risk of food insecurity and just over a quarter of all adults (26%) are food insecure.^[14] Approximately 70% of patients (*n*=100) admitted to a specialist tuberculosis hospital in Mpumalanga were from food-insecure households (J Wessels, unpublished data). Patients with tuberculosis also incur substantial direct (e.g. transport to and from the clinic for consultation and treatment) and indirect (e.g. time and income loss due to absence from work) costs related to their condition,^[15] further exacerbating the social inequity. Currently, only 5% of all tuberculosis patients access the disability grant provided through the South African Social Security Agency.^[15] Improving access to the disability grant, as well as a possible expansion thereof to tuberculosis patients contingent on treatment adherence or other relevant improved health behaviours associated with tuberculosis risk (e.g. stopping smoking),^[16] along with effective implementation of nutritional supplementation when indicated, deserves due attention in the fight to improve the concomitant and intergenerational burden of poor nutrition and tuberculosis in SA.

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