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Nutritional supplements for patients being treated for active visceral leishmaniasis (Review)

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[Intervention Review]

Nutritional supplements for patients being treated for active visceral leishmaniasis

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ABSTRACT

Background

Visceral leishmaniasis (VL) is a disease caused by a parasite, which can lead to death if untreated. Poor nutritional status hastens the progression of VL infection, and VL worsens malnutrition status. Malnutrition is one of the poor prognostic factors identified for leishmaniasis. However, the effects of nutritional supplementation in people treated for VL are not known.

Objectives

To assess the effects of oral nutritional supplements in people being treated with anti-leishmanial drug therapy for VL.

Search methods

We searched the Cochrane Infectious Diseases Group (CIDG) Specialized Register, CENTRAL, MEDLINE, Embase, LILACS, and two trial registers up to 12 September 2017. We checked conference proceedings and WHO consultative meeting reports, the reference lists of key documents and existing reviews, and contacted experts and nutritional supplement companies.

Selection criteria

Randomized controlled trials (RCTs), quasi-randomized controlled trials (quasi-RCTs), and non-randomized controlled trials (NRCTs) of any oral nutritional supplement, compared to no nutritional intervention, placebo, or dietary advice alone, in people being treated for VL.

Data collection and analysis

Two review authors independently screened the literature search results for studies that met the inclusion criteria. We had planned for two review authors to independently extract data and assess the risk of bias of the included studies. We planned to follow the Cochrane standard methodological procedures for assessing risk of bias and analysing the data.

Main results

We identified no eligible studies for this review, either completed or ongoing.

Authors' conclusions

We found no studies, either completed or ongoing, that assessed the effects of oral nutritional supplements in people with VL who were being treated with anti-leishmanial drug therapy. Thus, we could not draw any conclusions on the impact of these interventions on primary cure of VL, definitive cure of VL, treatment completion, self-reported recovery from illness or resolution of symptoms, weight gain, increased skinfold thickness, other measures of lean or total mass, or growth in children.

This absence of evidence should not be interpreted as evidence of no effect for nutritional supplements in people under VL treatment. It means that we did not identify research that fulfilled our review inclusion criteria.

The effects of oral nutritional supplements in people with VL who are being treated with anti-leishmanial drug therapy have yet to be determined by rigorous experimental studies, such as cluster-randomized trials, that focus on outcomes relevant for patients.

PLAIN LANGUAGE SUMMARY

Nutritional supplements for patients who are being treated for active visceral leishmaniasis

What is the aim of this review

The aim of this Cochrane review was to find out whether oral nutritional supplements could help people who were being treated for visceral leishmaniasis (VL). We tried to collect and analyse all relevant studies that answered this question.

Key messages

We found no trials, either completed or ongoing, that answered our review question. Thus, good quality evidence on the effects of oral nutritional supplements in people who are being treated with anti-leishmanial drug therapy is needed. This evidence could be obtained if a large, well done, randomized clinical trial was undertaken.

What was studied in this review

VL, also known as kala-azar, is an infection that has a worldwide distribution. It can lead to death if untreated. Malnutrition and VL are interconnected health problems. On the one hand, malnutrition may hasten the progression of the infection, while on the other hand, VL worsens the malnutrition status of the individual. Also, if a person with VL is malnourished, she or he does not respond as well to the treatment for leishmaniasis. As VL frequently affects people living in poor countries, with limited access to optimal diets, giving additional nutrients to people receiving treatment for VL may improve their nutrition, and thus, their health.

We searched for trials that evaluated the effects of providing any oral nutritional supplement, compared with placebo, dietary advice, or no nutritional intervention, in people who were being treated for VL.

What are the main results of this review?

We found no trials, either completed or ongoing, that answered our review question. Thus, there is no high quality evidence from trials to inform healthcare professionals about the effects of oral nutritional supplements in people who are being treated for VL.

This absence of evidence should not be interpreted as evidence of no effect for nutritional supplements in people under VL treatment. It means that we did not identify any eligible research for this review, and that the effects of oral nutritional supplements have yet to be determined by rigorous studies.

How up-to-date is this review

We searched for studies that had been published up to 12 September 2017.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Nutritional supplements versus no nutritional supplements for people who are being treated for active VL

Patient or population: people who are being treated for active VL
Setting: any
Intervention: nutritional supplements
Comparison: no nutritional supplements

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no nutritional supplements	Risk with nutritional supplements				
Primary cure	No trials met the inclusion criteria. Thus, there is no data for this outcome		-	(0 RCTs)	-	-
Definitive cure	No trials met the inclusion criteria. Thus, there is no data for this outcome		-	(0 RCTs)	-	-
Treatment completion	No trials met the inclusion criteria. Thus, there is no data for this outcome		-	(0 RCTs)	-	-
Self-reported recovery from illness or resolution of symptoms	No trials met the inclusion criteria. Thus, there is no data for this outcome		-	(0 RCTs)	-	-
Weight gain, increased skinfold thickness, or other measures of lean or total mass, or growth in children	No trials met the inclusion criteria. Thus, there is no data for this outcome		-	(0 RCTs)	-	-
Adverse outcomes	No trials met the inclusion criteria. Thus, there is no data for this outcome		-	(0 RCTs)	-	-

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Abbreviations: CI: confidence interval; VL: visceral leishmaniasis; RCT: randomized controlled trial; RR: risk ratio; OR: odds ratio.

BACKGROUND

Description of the condition

The leishmaniases are a group of diseases caused by protozoan parasites of the genus *Leishmania*. The parasite is transmitted by bites of the insects from the Diptera family, genus *Phlebotomus* and *Lutzomya* (also called sandflies), which are infected with the *Leishmania* parasite.

Leishmaniasis can have many different clinical presentations, including subclinical (or unapparent) infection, localised skin lesions (solitary or limited cutaneous leishmaniasis), and disseminated infection (cutaneous, mucosal, or visceral leishmaniasis (VL)), which are associated with a variety of signs, symptoms, and degrees of severity (Murray 2005). For the purpose of this Cochrane Review, we focused solely on VL.

VL is considered a "tool-deficient" disease in terms of control, which means that the available tools for the control of the disease are inadequate for scaling up campaigns, can be very costly, and require specially-trained staff and strong logistical support (WHO/The Carter Center 2008).

Clinical features of VL

The amastigote form of the *Leishmania* parasite attacks the reticuloendothelial system of naive people. This lowers the immunity of the infected person and causes limited infections that either spontaneously resolve or progress over weeks and months with persistent fever, anaemia, cough, abdominal pain, diarrhoea, enlargement of the liver and spleen (hepatosplenomegaly), weight loss, bleeding from the nose (epistaxis) due to decreased platelets (thrombocytopenia), depleted blood counts (pancytopenia), susceptibility to secondary infections, and also to death if disease is untreated. Signs of malnutrition (oedema, skin, and hair changes) develop as the disease progresses (Murray 2005; WHO 2010).

Specific disease symptoms may differ from region to region; for example, darkening of the skin of the face, hands, feet, and abdomen is typically found in patients of the Indian subcontinent (the Hindi name, kala-azar, means 'black fever' or deadly fever). Also, if the patient's immune system is reconstituted, VL may evolve to a skin condition known as post-kala-azar dermal leishmaniasis (PKDL; Zijlstra 2003).

VL and immunosuppression

VL is also an opportunistic infection in people living with HIV or other immunosuppressed patients (Alvar 2008; van Griensven 2014). Active VL may represent a relapse (recurrence six to 12 months after apparently successful treatment) or late reactivation of a subclinical or previously-treated infection. Reactivation can be spontaneous, but can also occur due to a reduction in T-cell (CD4) number or function due to immunosuppressive drugs and in people living with advanced HIV disease (Alvar 2008).

The increased prevalence of HIV in the last three decades has made the treatment and control of leishmaniasis more important, as the two infections are closely associated in many parts of the world, and issues of prevention and control are of global public health importance (Alvar 2008).

Causes and impact

The estimated global annual incidence of VL is 0.2 to 0.4 million people, and 90% of the cases occur in just six countries: India, Bangladesh, Sudan, South Sudan, Ethiopia, and Brazil (Alvar 2012). VL causes an estimated 20,000 to 40,000 deaths annually (a rate surpassed among parasitic diseases only by malaria), and 357,000 disability-adjusted life years lost (DALYs), which places leishmaniasis ninth in a global analysis of infectious diseases (Hotez 2004). Incidence of VL is sharply declining in the Indian subcontinent due to various reasons, including the natural trend and the kala-azar national elimination program (NVBDCP Programme 2017).

VL may be endemic, sporadic, or epidemic. In areas endemic for VL, the disease tends to be relatively chronic, and children, in particular, are affected. Sporadic VL may occur in non-native people of any age who enter an endemic area. In epidemic VL, people of all ages are susceptible, except those who acquired immunity previously. Acute cases of the disease can occur, and mortality is usually high.

In the Old World, VL is caused by *Leishmania donovani* and *Leishmania infantum* parasite species. Most infections are asymptomatic (almost 90%), and longitudinal studies have shown that depending on host condition (malnutrition, immune suppression, and others), the infected person may develop clinical disease (Badaró 1986; Ferreira 2018). In Old World endemic areas, the most affected age group has traditionally been children aged between one and four years (Harhay 2011). However in Europe, since the advent of HIV infection and increased use of immunosuppressive therapies for transplantation and chemotherapy, about half of the VL cases occur in adults (Carrillo 2015). Nevertheless, in endemic areas of East Africa and India, the highest incidence remains in children and young adults (Alvar 2012; Harhay 2011). PKDL occurs in areas endemic for *L. donovani*, but is more common in East Africa and in Asia, where up to 50% in East Africa and up to 10% to 20% of VL patients in Asia will develop the condition after treatment (Zijlstra 2003; Zijlstra 2017).

In the New World, the etiological agent is *L. infantum*. Most cases occur in children under 10 years of age, but adults are also frequently affected because of recent introduction of the organism. PKDL is extremely rare. Longitudinal follow-up has shown that some people remain asymptomatic or recover spontaneously from mild disease, while others with these conditions eventually develop clinical VL. Risk factors for progression to VL include malnutrition and other infectious diseases (Badaró 1986; Ferreira 2018).

Diagnosis of VL

Clinical diagnosis

The clinical characteristics of VL are: persistent fever (more than two weeks) not due to malaria, tuberculosis, or other infections (unresponsive to a course of antibiotics); splenomegaly; and weight loss. In people living with HIV, the clinical features of VL may be atypical. The isolated or combined presence of anaemia, leukopenia, thrombocytopenia, or polyclonal hypergammaglobulinaemia reinforces the clinical suspicion but lacks diagnostic accuracy.
Therefore, *Leishmania*-specific laboratory tests are required for diagnostic confirmation.

Parasitological diagnosis

Parasitological confirmation should be based on microscopy and demonstration of the parasite through morphological identification or cultured parasites from aspirates of spleen, bone marrow, or lymph nodes (the later mainly valid in East Africa), or molecular biological methods, such as polymerase chain reaction (PCR), or both.

Serological diagnosis

Serological confirmation should be based on the use of specific anti-*Leishmania* antibodies. Among various options, the most feasible and recommended technique is rk39-based immuno chromatographic test, which in case of doubtful results, should be combined with a second serological test, like direct agglutination test (DAT), immunofluorescence antibody test (IFAT), or enzyme-linked immunosorbent assay (ELISA; (Boelaert 2014; WHO 2010)).
All serological tests suffer from two limitations. First, specific antibodies remain detectable up to several years after cure of the infection. Therefore, relapse cannot reliably be diagnosed by serology. Second, a proportion of healthy people living in VL-endemic areas with no history of VL may show low positive titers for anti-*leishmanial* antibodies, due to asymptomatic infection or cross-reactions with other diseases. Therefore, antibody-based tests must always be used in combination with a standardized clinical case definition for VL diagnosis (WHO 2010).

Treatment of VL

Treatment should be given only after confirmation of the disease. The extent of concomitant infection should be ascertained, as this may influence the choice of therapy or supportive treatment. In many cases, supportive treatment and patient stabilization, for example rehydration or nutritional supplementation, are essential before starting the therapy, and may also decrease drug toxicity.
For the past seven decades, pentavalent antimonials have been the standard first-line treatment for people with VL, and amphotericin B deoxycholate and pentamidine have been the second-line treatment. In the past 10 years, lipid formulations of amphotericin B, miltefosine, and paromomycin have been approved for VL treatment. The risk of developing resistance to monotherapy is the main reason combined medications are recommended (van Griensven 2014).
Ideally, VL treatment should cure the patient, reduce the risk for relapse and for PKDL, and avoid the development of resistance. Successful therapy improves the general condition and weight of the person, resolves fever, causes regression of splenomegaly, and recovery of normal blood counts. An initial cure can be declared if there is clinical improvement at the end of treatment. Complete regression of splenomegaly may take several months. A good indicator of definitive cure is the absence of clinical relapse at six months, although relapses can occur later.
Poor prognostic factors in response to VL treatment are age over 45 years (in Africa), malnutrition, renal and hepatic comorbidity, concomitant infections, such as pneumonia, tuberculosis, or HIV infection, or other immunosuppressive conditions (WHO 2010).

Description of the intervention

Nutrition interventions can broadly be divided into macronutrients (carbohydrates, protein, and fat), and micronutrients (essential vitamins and trace elements).

Macronutrients

The energy requirements of a 70 kg adult male to maintain body weight and composition are approximately 2550 kilocalories (kcal) per day, ideally consumed as 55% carbohydrate, 15% protein, and 30% fat (FAO/WHO/UNICEF 2001).
If it was shown that people with active VL required additional macronutrients, these could be purchased and consumed by the patient simply by following nutritional advice. However, leishmaniasis has strong links with poverty, and usually affects people from the poorest segments of the population. Therefore, in many situations, especially in resource-limited settings, the person may not be able to acquire this additional food, due to economic hardship or local food insecurity (Alvar 2006). In these situations, healthcare services might provide increased nutrients through free provision of meals, take-home rations, or specific high-energy supplements. United Nations International Children's Emergency Fund (UNICEF) provides therapeutic feeding to children under five years of age with VL, but only if they suffer from severe, acute malnutrition. In East African countries, in which up to 40% of the VL patients are malnourished, only non-governmental organizations (NGOs) can supplement food as part of their VL treatment programmes. Moreover, although medicines for the treatment of people with VL are given free of cost for VL patients treated by the Ministry of Health within the national programmes, patients must pay for concomitant treatments, diagnostics, and in-hospitalizations costs, including food.

Micronutrients

The daily micronutrient requirements for individuals vary greatly by age and gender (Food and Nutrition Board 2006).

These requirements can be gained from the consumption of a healthy and varied diet, or through pharmaceutical supplementation as tablets, capsules, or powders. Any additional requirements could be gained through increased consumption following dietary advice, or through pharmaceutical provision via the health service.

In trials of macronutrient and micronutrient interventions, the following two important factors should be noted.

- The intervention is a supplement and does not represent the total daily intake of that nutrient.
- Any benefit derived from the intervention is likely to be dependent on the initial nutritional status of the patient.

In order to accurately interpret the data, it is therefore essential to consider both the baseline (before starting the intervention) nutritional status, and the overall nutritional intake of the patients.

How the intervention might work

Malnutrition takes many forms, but in the regions affected by VL, it most commonly refers to inadequate protein and energy intake (protein energy malnutrition, or PEM), in association with multiple micronutrient deficiencies. These two nutritional problems are one of the major health burdens in developing countries.

As already described, VL is mainly found among poor communities, in which diets are frequently inadequate to meet the recommended daily requirements. Malnutrition is also more pronounced in individuals with infection or advance disease, as a consequence of reduced nutrient intake, increased nutritional needs, and excessive losses due to diarrhoea, malabsorption, and parasitic infections. In these communities, a high prevalence of poor diet and infectious disease regularly converges into a vicious cycle.

Observational studies have suggested that both PEM and micronutrient deficiencies may hasten the progression of leishmaniasis infection (Anstead 2001; Cerf 1987; Collin 2004; Dye 1993), and that VL worsens malnutrition (Luz 2001; Van Weyenbergh 2004). The leishmaniasis infection and malnutrition 'vicious cycle' of immune dysfunction, infectious disease, and malnutrition has already been described (Malafaia 2009; Serafim 2010).

Harhay 2011 analysed the nutritional data of 29,750 VL patients from six of the most endemic foci of VL (Brazil, India, Nepal, Sudan, South Sudan, and Uganda). In some of the study sites, up to 25% of them had severe acute malnutrition and 40% were underweight. This study also noted that supplementary and therapeutic feeding interventions for VL patients were generally in place in treatment sites run by NGOs, but were often lacking in governmental centres.

Malnutrition and VL are interconnected health problems. It is difficult to evaluate to what extent malnutrition is either a risk factor for, or the result of, VL.

Therefore, the inclusion of nutrient supplementation in the treatment of active VL could improve morbidity and mortality outcomes of the disease, by doing the following.

- Improve VL treatment outcomes by restoring cell-mediated immunity, increasing the individual's ability to fight the infection, and hastening recovery from the illness.
- Promote nutritional recovery with increased weight gain in adults, and weight gain and growth in children.

Notably, pathogens such as *Leishmania* also require certain micronutrients for their own metabolism, and greater availability of these nutrients through supplementation could encourage their growth. There is some evidence for this regarding vitamin C and vitamin E supplementation (Garg 2004), and pantothenic acid (vitamin B5) supplementation (Actor 1960). Therefore, nutritional interventions cannot be considered entirely benign.

Why it is important to do this review

There is no evidence-based guidance on food provision or supplementation for adults or children being treated for VL, with or without concurrent HIV infection. This Cochrane Review attempted to assess the evidence for the effectiveness of different food and nutritional supplements in helping people to recover from VL, and to highlight where more research might be needed.

OBJECTIVES

To assess the effects of oral nutritional supplements in people being treated with anti-leishmanial drug therapy for VL.

METHODS

Criteria for considering studies for this review

Types of studies

We considered the following study designs, with allocation at either the individual or cluster level.

- Randomized controlled trials (RCTs): a trial in which the trial investigator prospectively allocates each participant (or group of participants) to an intervention or to a control arm using a process of random allocation (for example, random number generation or coin flips).
- Quasi-randomized controlled trials (quasi-RCTs): a non-randomized trial in which the investigator prospectively allocates each participant (or group of participants) to an intervention or to a control arm using a process that attempts, but does not

achieve, true randomization (for example, alternation of allocation, birth dates, or weekdays).

- Non-randomized controlled trials (NRCTs): a non-randomized study in which the investigator prospectively allocates each participant (or group of participants) to an intervention or to a control group (or more) using a process that is clearly not random (for example, allocation by judgement of the clinician, or by preference of the participant).

Types of participants

We considered people of all ages, with or without human immunodeficiency virus (HIV) infection, and being treated for VL.

Types of interventions

Intervention

We considered any oral nutritional supplement given in addition to any anti-leishmanial drug treatment. We excluded trials that assessed tube feeding or parenteral nutrition, as well as trials that assessed dietary advice alone, without the actual provision of supplements.

Control

No nutritional intervention, placebo, or dietary advice alone.

Types of outcome measures

Primary outcomes

- Primary cure (clinical and parasitological improvement after treatment), defined as the absence of parasites at the end of treatment, resolution of clinical signs and symptoms of VL (defervescence, weight gain, and decrease in spleen size), and absence of clinical signs attributable to PKDL.

Secondary outcomes

- Definitive cure, defined as confirmed cure at the end of treatment, with no VL signs or symptoms, or clinical signs of PKDL, which require rescue treatment, within six months of follow-up.
- Treatment completion.
- Self-reported recovery from illness or resolution of symptoms.
- Weight gain, increased skinfold thickness, or other measures of lean or total mass.
- In children, any measure of growth: improvement of height for age, weight for height, weight for age, body mass index (BMI) for age, or any other nutritional indicator used as baseline measure at start of treatment.

Adverse outcomes

- No cure, defined as any of the following situations (or a combination among them): no clinical improvement during treatment or after treatment completion, no parasitological cure (parasitology remains positive), or need of rescue medication.
- Death from any cause.
- Relapse, defined as a patient who had an initial cure, but presented with VL signs and symptoms after treatment, up to six-month follow-up, patient required rescue medication.

Search methods for identification of studies

We attempted to identify all relevant studies, regardless of language or publication status (published, unpublished, in press, or ongoing).

Electronic searches

Databases

We searched the following databases for relevant studies, using the search terms and strategies detailed in Appendix 1: the Cochrane Infectious Diseases Group (CIDG) Specialized Register (12 September 2017); the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 9), in the Cochrane Library (12 September 2017); MEDLINE (PubMed, 1966 to 12 September 2017); Embase OVID (1980 to 12 September 2017); LILACS (Latin American and Caribbean Health Science Information database; 1982 to 12 September 2017).

On 17 September 2017, we also searched the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/en/); and ClinicalTrials.gov (clinicaltrials.gov), using leishmania, leishman*, and leishmaniasis as search terms.

Searching other resources

Conference proceedings

We searched the following conferences proceedings for relevant abstracts.

- 1^{st} World Congress on Public Health, 2006 September 20-28; Barcelona, Spain.
- 2^{nd} World Congress on Public Health, 2010 September 23-25; Oporto, Portugal.
- 3^{rd} World Congress on Public Health, 2014 November 9-11; Las Palmas de Gran Canaria, Spain.
- 18^{th} International Nutrition Congress, 2005 September 20-23; Durban, South Africa.
- 19^{th} International Nutrition Congress, 2009 September 4-9; Bangkok, Thailand.

- 20^{th} International Nutrition Congress, 2013 September 15-20; Granada, Spain.
- 3^{rd} World Congress on Leishmaniasis, 2005 April 10-15; Palermo, Italy.
- 4^{th} World Congress on Leishmaniasis, 2009 February 3-7; Lucknow, India.
- 5^{th} World Congress on Leishmaniasis, 2013 May 13-17; Pernambuco, Brazil.
- 6^{th} World Congress on Leishmaniasis, 2017 May 16-20; Toledo, Spain.

Consultative meetings reports

We screened the following WHO reports: WHO 2010; WHO 2013; WHO 2014a; WHO 2014b; WHO 2014c; WHO 2014d; WHO 2014e; WHO 2015a; WHO 2015b; WHO 2016a; WHO 2016b; WHO 2016c; WHO 2016d; WHO 2017a; WHO 2017b; WHO 2017c; and WHO 2017d.

Researchers

We contacted key authors in the field and the authors of similar systematic reviews. We had planned to contact the authors of studies included in the review, and of ongoing studies identified in the different clinical trials registration systems.

Companies

On the 27 November 2017, we contacted the following companies for unpublished and ongoing trials: AkzoNobe, DSM Nutritional Products, Nestle, Nutergia, and Taiyo International.

Reference lists

We also checked the reference lists of key documents and existing reviews (Bush 2017; Chappuis 2007; Cheeran 2010; Elmahallawy 2015; Freitas-Junior 2012; Olliaro 2005).
See the 'Differences between protocol and review' section.

Data collection and analysis

Selection of studies

At least two review authors (EC, JA, JLA, and SSgB) independently screened all citations and abstracts identified by the search strategy to identify potentially eligible studies. We obtained the full-text articles of potentially eligible studies. At least two review authors (EC, JLA, and SSgB) independently assessed these articles for inclusion, using a predefined eligibility form, based on the inclusion criteria. We had planned to contact the study authors for clarification in the event that it was unclear whether a trial was eligible for inclusion in the review. If there was no consensus between the two review authors involved in the screening of titles and abstracts, or in the assessment of the full-texts, we consulted a third review author. We used Covidence to implement the selection process (Covidence 2017).
We excluded studies that did not meet the inclusion criteria, and documented the reasons for the exclusion of the full texts assessed.

Data extraction and management

We foresaw that at least two review authors (EC, JLA, or MH) would independently extract data from each included study, using tailored and pre-tested data extraction forms. We had planned to extract data on study design, participant characteristics, interventions, and outcomes.
For dichotomous data, we had planned to extract the number of participants with at least one event, and the total number of participants in each treatment arm. For continuous outcomes, we had planned to extract the number of participants, the arithmetic mean, and the standard deviation (SD) for each group. If trial authors had reported median values, we had planned to extract ranges or interquartile ranges.
If the included trials had reported time-to-event outcomes, we had planned to extract the estimates of the log hazard ratio (HR) and its standard error (SE). If SEs had been unavailable, we had planned to extract alternative statistics, such as confidence intervals (CIs) or P values.
In cases of skewed continuous data, we had planned to extract geometric means, where presented by the study author.
For cluster-RCTs that adjust for clustering, the ideal information to extract would have been a direct estimate of the required effect measure with its CI, or measure of variation. In addition, for cluster-RCTs that did not adjust for clustering, we had planned to extract the average size of each cluster and the intra-cluster correlation coefficient (ICC), and we had planned to adjust these data using available methods, such as the effective sample size or the inflated variance (Higgins 2011). If the ICC had been unknown, we would have tried to make an estimation from external sources, such as trials with similar cluster sizes and features. Once we had adjusted trials, we had planned to combine the data in a meta-analysis. If we had been unable to adjust these trials, we had planned to exclude these data from the meta-analysis.

Assessment of risk of bias in included studies

Two review authors (EC, MH, or JLA) had planned to independently assess the risk of bias of each included RCT using the Cochrane 'Risk of bias' assessment tool (Higgins 2011). We had planned to assess the following six components for each included trial: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other biases. For each of these components, we had planned to assign a judgment on the risk of bias of either 'yes' (low risk of bias), 'no' (high risk of bias), or 'unclear' (unclear risk of bias). We had

planned to contact the trial authors for clarification if any of the six components were unclear, or not stated in the report. We had planned to record the results in the 'Risk of bias' tables in Review Manager 5 (RevMan 5), and to summarize the findings as a 'Risk of bias' table or graph (RevMan 2014).

To assess the risk of bias of the non-randomized trials eligible for this review (that is, quasi-RCTs and non-randomized-RCTs) we had planned to use the ROBINS-I tool (Sterne 2016a), and follow the guidance detailed in Sterne 2016b (see the 'Agreements and disagreements with other studies or reviews' section).

Measures of treatment effect

We had planned to compare dichotomous outcomes using risk ratios (RR) and their 95% CIs. For continuous data reported as arithmetic means and SDs, we had planned to combine them using the mean difference. Where included studies reported continuous data using geometric means, we had planned to combine these data on the log scale, using the generic inverse variance method, and report them on the natural scale; we had planned to report the medians and ranges in a table. We had planned to present all results with 95% CIs.

Unit of analysis issues

For trials that included more than two comparison groups, we had planned to split and analyse them as individual pair-wise comparisons.

If included studies had reported count data, we had planned to extract the total number of events in each group, and the total amount of person-time at risk in each group. We had planned also to record the total number of participants in each group. If this information had been unavailable, we had planned to extract alternative summary statistics, such as rate ratios and CIs, if available. For studies presenting count data as dichotomous outcomes, we had planned to extract the number of participants in each intervention group, and the number of participants in each intervention group who experienced at least one event.

Dealing with missing data

We had planned to obtain missing data from the authors of the included trials. Where possible, we had planned to extract data to allow an intention-to-treat (ITT) analysis, in which we would have analysed all randomized participants in the groups to which they were originally assigned. If there had been any discrepancy in the number of participants randomized and the numbers analysed in each treatment group, we had planned to calculate the percentage lost to follow-up in each group, and report this information. If people lost to follow-up had exceeded 10% for any trial, we had planned to assign the worse outcome to those lost to follow-up for dichotomous outcomes (except for the outcome of death), and assess the impact of this in sensitivity analyses, with the results of completers.

For continuous data with missing SDs, we had planned to either calculate these SDs from other available data, such as SEs, or to impute them, using methods suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We would not have made any assumptions about losses to follow-up for continuous data, and we had planned to analyse the results for those participants who had completed the trial.

Assessment of heterogeneity

We had planned to assess heterogeneity between the included trials by visual examination of the forest plot to check for overlapping CIs, using the Chi² test for heterogeneity with a 10% level of significance, and the I^2 statistic. We had planned to use an I^2 statistic value of 50% or greater to denote significant heterogeneity. If this value had been substantial (75% or greater), we would not have attempted data synthesis if we couldn't explain heterogeneity by clinical or methodological features of the trial, or by subgroup analyses (see the 'Subgroup analysis and investigation of heterogeneity' section).

Assessment of reporting biases

We had planned to assess the likelihood of publication bias by examining a funnel plot for asymmetry due to small study effects, provided that there were at least 10 included trials.

Data synthesis

We had planned to synthesize dichotomous data using pooled and weighted risk ratios (RR). We had planned to combine continuous data, summarized by arithmetic means and SDs, using mean differences. If study authors had summarized continuous data by using geometric means, we had planned to combine them on the log scale, using the generic inverse variance method, and to report them on the natural scale. We had planned to compare count data using rate ratios, when the total number of events in each group and the total amount of person-time at risk in each group was available, by RR if data had been presented in dichotomous form, or mean difference if data were presented in continuous forms. We had planned to combine the HRs from survival data on the log scale, using the inverse variance method, and to present these data on the natural scale.

Subgroup analysis and investigation of heterogeneity

We had planned to use a fixed-effect model to synthesize data when there was no heterogeneity. We had planned to combine the trials using a random-effects model when heterogeneity was present, but not substantial (I^2 statistic greater than 50%, but less than 75%), or when it could not be explained by subgroup analyses, or by clinical or methodological features of the trials and the participants. If we had found substantial heterogeneity, or substantial differences across the trials in clinical or methodological features, we had

planned to present the trials in a forest plot, but not combine them in a meta-analysis. If data had permitted, we had planned to perform subgroup analysis, considering the following factors:

- HIV-positive people.
- Malnourished individuals.
- Nutritional supplements.
- Drug treatments.
- Geographical region.
- Age.
- Sex.

Sensitivity analysis

We had planned to undertake sensitivity analyses if trials reported dropout rates of 10% or greater, to ascertain differences in outcomes with ITT analyses, and analyses of completers.

For included cluster-RCTs, we had planned to follow the CIDG cluster-RCT guide checklist (cidg.cochrane.org/sites/cidg.cochrane.org/files/public/uploads/cluster_randomised_trials_guide_feb2010.doc). If study authors had estimated ICC, we had planned to perform sensitivity analyses by excluding trials that did not originally adjust for clustering, to see if the results of the meta-analysis changed. When study authors did not report ICC, and we couldn't calculate it manually to give an approximate value, we had planned to perform sensitivity analyses using a range of estimates for the ICC, to see if clustering could influence the individual trial's result.

RESULTS

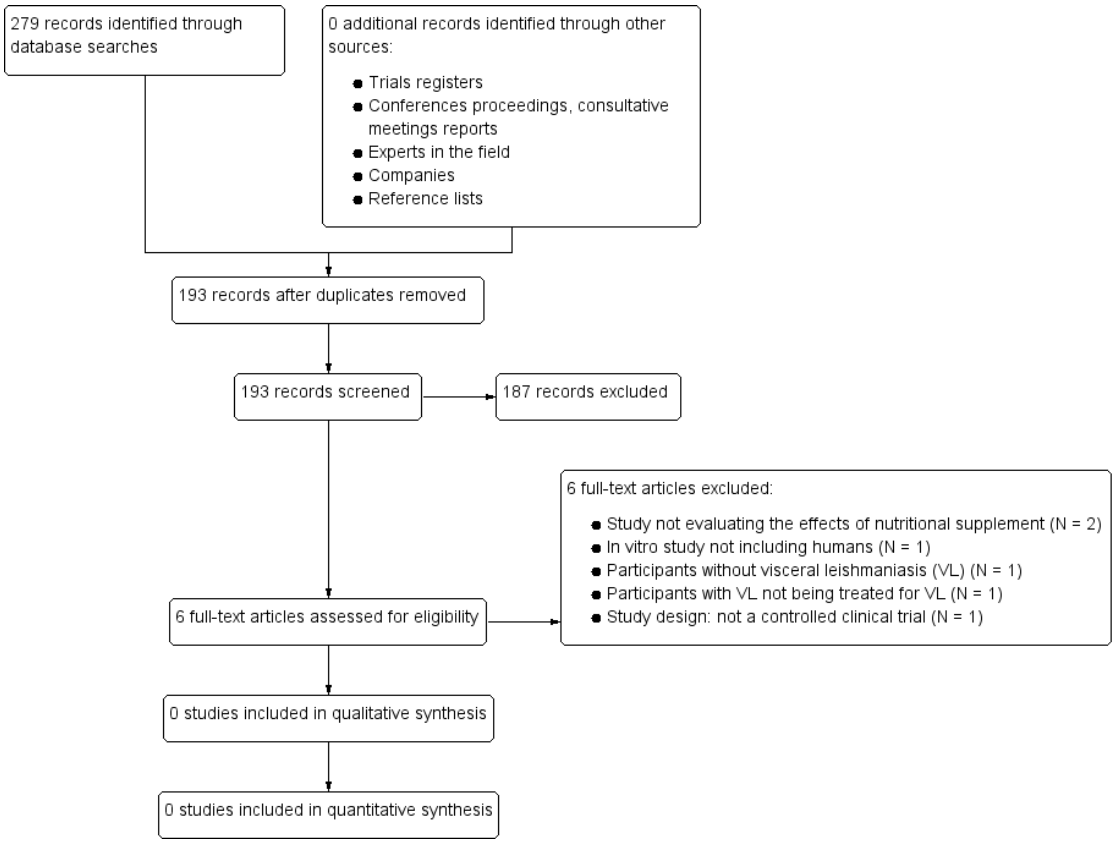
Description of studies

Results of the search

Following removal of duplicates, the search strategy of the electronic databases to 12 September 2017 generated 193 records. We examined the titles and abstracts of these records to assess their potential relevance, and we subsequently retrieved six full-texts for further examination. We did not identify any studies that met the eligibility criteria.

We did not find any eligible study, either completed or ongoing, by searching trial registries. We found no references by checking the abstracts of relevant conferences or meetings, reference lists of key documents, or through personal contact with experts in the field or nutritional supplement companies. See the study flow diagram, which follows the template described in the PRISMA statement (Figure 1; Liberati 2009).

Figure 1. Study flow diagram



Included studies

We found no eligible studies for this review, neither completed nor ongoing.

Excluded studies

We excluded all six records after full-text assessment (Aruoma 2006; Croft 1985; Diro 2015; Duke 2011; Maciel 2014; Thakur 2010). We summarized the reasons for their exclusion in the flow diagram (Figure 1) and in the 'Characteristics of excluded studies' table.

We excluded NCT01069198, an ongoing trial on the efficacy of a combination of anti-helminth, and vitamin A, zinc, and iron supplementation in preventing active VL among individuals with asymptomatic VL. The control group of this trial received placebo without an active treatment for VL (for a study to be eligible both study groups had to receive active treatment for VL).

Risk of bias in included studies

No studies met the eligibility criteria, so we could not assess risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Nutritional supplements versus no nutritional supplements for people who are being treated for active visceral leishmaniasis (VL)

We did not find any trial that assessed the effects of oral nutritional supplements in people who were being treated with anti-leishmanial drug therapy for VL. See 'Summary of findings' table 1 (Summary of findings for the main comparison).

DISCUSSION

Summary of main results

We did not find any eligible studies, either completed or ongoing, for this review. Consequently, we could not determine the effects of oral nutritional supplements in people who were being treated with anti-leishmanial drug therapy for VL.

Overall completeness and applicability of evidence

Completeness of the evidence

No trials met our inclusion criteria. Thus, the evidence base for the effects of oral nutritional supplements in people being treated with anti-leishmanial drug therapy for VL is incomplete.

We were surprised by the lack of studies that met our inclusion criteria, and by the low number of records generated by the searches in electronic databases (only 193 references after eliminating duplicates), as the topic area is not immature, and the leishmaniasis infection and malnutrition 'vicious cycle' of immune dysfunction, infectious disease, and malnutrition has already been described (Malafaia 2009; Serafim 2010). However, the lack of studies may be explained by several factors.

First, leishmaniasis is considered a neglected disease, that is, a group of diseases characterised by their association with poverty, and their proliferation in tropical environments (Alvar 2006; WHO 2007). Therefore, resources allocated to the study of the disease, or implementation of programmes to combat related factors, have been scarce compared to other diseases, which can help to explain the low number of references retrieved in the search strategy of this review (WHO 2012).

Second, we had planned to disentangle the effects of nutritional supplements given in addition to any anti-leishmanial drug treatment. Thus, we excluded studies that did not consider the nutritional supplementation as the only difference between study arms. That is, for a study to be included, the anti-leishmanial drug treatment had to be the same in the study arms, and no other condition except for the nutritional supplementation could differ between them.

Third, the methodological challenges associated with the evaluation of nutritional interventions may hamper the realization of these trials. As an example, nutritional interventions are usually implemented in addition to other interventions, which makes them 'complex interventions', that is, interventions with several interacting components. Complex interventions present several special problems for evaluators, in addition to the practical and methodological difficulties that any successful evaluation must overcome (MRC 2008). Moreover, conducting RCTs in the contexts where VL and malnutrition are highly prevalent, such as South Sudan, is challenging.

Fourth, we restricted our review to controlled clinical trials, either randomized or not. Therefore, we excluded observational studies, which are common in the field of nutrition research, because of an inherently high risk of selection and detection biases (Ortiz-Moncada 2011).

Applicability of the evidence

Applicability of the evidence is the assessment of whether the findings of a review can be applied in a particular context or population (Burford 2013). We could not assess the applicability of the evidence of this review, as we did not find any eligible studies.

Quality of the evidence

We identified no relevant studies that met the inclusion criteria of this review. Thus, we were unable to comment on the certainty of the evidence for this clinical question.

Potential biases in the review process

Search methods for identification of studies

We performed searches as extensively as possible, in order to reduce the risk of publication bias, and to identify as much relevant information as possible. The Information Specialist of the CIDG carefully designed the searches, without any language or date of publication restrictions. However, we may have lost some eligible studies, as the risk of publication bias in the field of nutrition research might be even higher than in drug research (Chartres 2016). On the other hand, we may have missed individuals or organizations that have conducted eligible RCTs, so we may not have identified relevant RCTs.

'Summary of findings' tables

In our protocol, we did not plan to create 'Summary of findings' tables, therefore, we chose the outcomes for the 'Summary of findings' tables after the protocol publication. However, we think that the outcomes we chose are relevant to support informed decisions.

Agreements and disagreements with other studies or reviews

As there are no included studies in this review, we were unable to locate any evidence that could be compared with other studies. We found no experimental studies conducted in humans on the topic, but there was a review that assessed the role of protein-energy malnutrition as a risk factor for VL, confirming malnutrition as a major determinant of both progression and severity of the disease (Malafaia 2009). However, this review did not assess

the effect of nutrient supplementation on VL patients. The existing experimental studies conducted in animal models have yielded conflicting results on nutritional components of the diets and the progression of VL in infected animals. More specifically, in terms of a) macronutrients and protein supplementation (Actor 1958; Anstead 2001; Ritterson 1949), and b) micronutrient supplementation such as vitamins (A, B-complex, and E) or minerals (iron and copper; Actor 1958; Actor 1960; Anstead 2001; Garg 2004). Some of these studies found an antagonistic relationship between the nutrient supplementation and the proliferation of the infection, while others found a synergistic association. Only in relation to the supplementation of vitamin C, zinc, and flavonoids, were the results consistent with the potential improvement of the prevention and progression of VL (Anstead 2001; Garg 2004; Mittra 2000; Van Weyenbergh 2004).

AUTHORS' CONCLUSIONS

Implications for practice

We found no studies, either completed or ongoing, that assessed the effects of oral nutritional supplements in people with visceral leishmaniasis (VL), treated with anti-leishmanial drug therapy. Thus, we cannot conclude on the impact of these interventions on primary cure of VL, definitive cure of VL, treatment completion, self-reported recovery from illness or resolution of symptoms, weight gain, increased skinfold thickness, or other measures of lean or total mass, or growth in children.

The absence of evidence should not be interpreted as the evidence of no effect for nutritional supplements in people under VL treatment. It means that eligible research for this review was not identified.

Implications for research

This is an 'empty review', that is, a review that has no included studies. This highlights the need for rigorous studies to determine the effects of oral nutritional supplements in people with VL, who are receiving anti-leishmanial drug therapy.

Randomized controlled trials (RCT) testing the effect of a specific nutrient are essential, as the randomized design is the only one that is able to demonstrate a causal relationship between a dietary change and health outcomes (Ioannidis 2016; Jakobsen 2013; Laville 2017; Maki 2014). However, RCTs of nutrients encounter additional barriers to those that affect the traditional drug RCTs (Laville 2017).

Table 1 details the nature of further research that would be most desirable, according to the 'Evidence - Population(s) - Intervention - Comparison - Outcomes - Time stamp' (EPICOT) format (Brown 2006).

Future RCTs should be rigorous in design and delivery. They should be adequately reported, which would enable appraisal and interpretation of results. Trials should be reported according to relevant reporting guidelines, such as: CONSORT statement (Schulz 2010); CONSORT extension for cluster-randomized trials (Campbell 2012); TIDieR checklist (Hoffmann 2014); or the reporting guidelines for health equity concerns in RCTs (Welch 2017). The Equator Library for health research reporting should be searched for pertinent reporting guidelines (Equator Network 2017).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aruoma 2006	Participants without VL.
Croft 1985	In vitro study that did not include humans.
Diro 2015	Study did not evaluate the effects of nutritional supplement
Duke 2011	Study design: not a controlled-clinical trial.
Maciel 2014	Participants with VL not being treated for VL.
NCT01069198	The control group received placebo rather than an active treatment for VL
Thakur 2010	Study did not evaluate the effects of nutritional supplement

Abbreviations: VL: visceral leishmaniasis.

ADDITIONAL TABLES

Table 1. Research recommendation

What are the effects of nutritional supplements in patients being treated for active visceral leishmaniasis (VL)? Evidence: we found no eligible studies for this systematic review.		
Elements	**Proposal**	**Comments**
Population	People being treated for VL	• Include all relevant participant groups, such as people with HIV. • Large, adequately powered trial. • Preferably multi-centre trial, in order to achieve adequate sample size (Laville 2017). • Stratify allocation according to age and basic nutritional status, to enable robust a priori subgroup analyses.
Intervention	Oral nutritional supplement	• If only a nutrient is tested, a placebo can be easily used, and a blinded RCT can be conducted (Laville 2017). • The study should be planned with

Table 1. Research recommendation (*Continued*)

		few interventions, to allow the effect of the micronutrient to be evaluated. • Provide details of all the interventions and co-interventions undertaken, of their compliance and their acceptability (Hoffmann 2014; MRC 2008). • In order to disentangle the effects of the nutrient on the outcome measure, the co-interventions must be similar in all study groups. • Compliance can be checked by counting pills, and possibly by assessing the nutrient concentration or related functions (Laville 2017).
Comparison	Placebo	
Outcomes	Relevant outcomes for key stakeholders defined, measured, collected, and reported in an objective, reliable, accurate, and actionable way	• To our knowledge, there is no 'core outcome set' (COS)[a] developed with a rigorous methodology for RCTs of nutritional supplements. • COS for RCTs of nutritional supplements should be developed with the method proposed in the COMET Handbook (Williamson 2017). • Blinding of patients, care givers and outcome assessment should be ensured with the use of placebo as a control group. The use of objective outcomes that are less susceptible to bias can also minimize the risk of detection bias (Lin 2012). • Relevant harms related to the use of nutrients should be specified beforehand, and should be assessed (Ioannidis 2004).
Study type	RCT	Cluster-RCTs (RCTs that randomize groups (clusters) rather than individuals) have several advantages compared to individual-RCTs (López-Alcalde 2015). For example, they may be less costly and time-consuming, as they simplify the logistics of implementation (Smith 2008); they control for confounding (Safdar 2008), and minimize treatment contamination[b] between intervention and control participants (Hayes 2000); they are better for measuring the overall group effect of an intervention, and for judging effectiveness (Hayes 2000), that

Table 1. Research recommendation (*Continued*)

		is, the extent to which a specific intervention, when used under ordinary circumstances, does what it is intended to do (Cochrane 2017). Moreover, they have broader generalizability. For example, cluster-RCTs minimize the Hawthorne effect, which is the effect on the people being studied (usually positive or beneficial), of being under study (Porta 2008).

Abbreviations: COS: core outcome set; HIV: human immunodeficiency virus; RCT: randomized controlled trial; VL: visceral leishmaniasis.

[a] Core outcome set: agreed standardized set of outcomes that should be measured and reported in all trials for a specific clinical area (Williamson 2012).

[b] Contamination: in a controlled trial, contamination is the inadvertent application of the intervention being evaluated to people in the control group, or the inadvertent failure to apply the intervention to people assigned to the intervention group (Cochrane 2017).

APPENDICES

Appendix 1. Search strategy

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	Embase[b]	LILACS[c]	WHO ICTRP	ClinicalTrials.gov
1	Leishman*	Visceral leishman* ti, ab	Visceral leishman* ti, ab	Visceral leishman* ti, ab	Leishman$	Condition: leishman*	Leishmania OR Leishmaniasis
2	Kala-azar	("Leishmaniasis, Visceral"[Mesh]) OR ("Leishmania donovani"[Mesh] OR "Leishmania infantum"[Mesh])	("Leishmaniasis, Visceral"[Mesh]) OR ("Leishmania donovani"[Mesh] OR "Leishmania infantum"[Mesh])	Visceral leishmaniasis [Emtree] OR Leishmania donovani [Emtree] OR Leishmania infantum [Emtree]	Kala-azar	-	-
3	kalaazar	Kala-azar or kalaazar ti, ab	Kala-azar or kalaazar ti, ab	Kala-azar or kalaazar ti, ab	kalaazar	-	-

(*Continued*)

4	1 or 2 or 3	1 or 2 or 3	1 or 2 or 3	1 or 2 or 3	1 or 2 or 3	-	-
5	Dietary supplement*	((("Dietary Supplements"[Mesh]) OR ("Micronutrients"[Mesh] OR "Trace Elements"[Mesh])) OR "Food, Fortified"[Mesh]) OR "Vitamins"[Mesh]	((("Dietary Supplements"[Mesh]) OR ("Micronutrients"[Mesh] OR "Trace Elements"[Mesh])) OR "Food, Fortified"[Mesh]) OR "Vitamins"[Mesh]	diet supplementation [Emtree] OR macronutrient [Emtree] OR trace element [Emtree] OR vitamin supplementation [Emtree] OR trace element [Emtree]	Dietary supplement$	-	-
6	Macronutrient*	-	Food supplement* ti, ab	Micronutrient ti, ab	Macronutrient$	-	-
7	Micronutrient*	-	Macronutrient* ti, ab	Fortified food* ti, ab	Micronutrient$	-	-
8	Vitamin*	-	5 or 6 or 7	Vitamin* ti, ab	Vitamin$	-	-
9	Trace element*	-	4 and 8	Food supplement* ti, ab	Trace element$	-	-
10	Food	-	-	5 or 6 or 7 or 8 or 9	Food	-	-
11	5 or 6 or 7 or 8 or 9 or 10	-	-	4 and 10	5 or 6 or 7 or 8 or 9 or 10	-	-
12	4 and 10	-	-	-	4 and 10	-	-

[a] Cochrane Infectious Diseases Group Specialized Register.
[b] Search terms used in combination with the search strategy for retrieving trials developed by Cochrane (Lefebvre 2011)
[c] Spanish and Portuguese synonymous terms were included.

CONTRIBUTIONS OF AUTHORS

Tasks	Authors
Protocol development	EC, JLA, MH, CB, CJ, TLC, AB, JA
Guarantor	EC
Contact person	EC
Piloted the selection stage	EC, JLA, JA
Screened titles and abstracts and assessed full texts	EC, JLA, MH, CJ, SSgB, JA
Assessed conferences	EC, CJ, MH, SSgB, TM, JA
Requested information to researchers and companies	EC, MH, TM
Designed the data extraction form	EC, JLA
Wrote the background	EC, JA
Wrote the methodological sections of the review	EC, JLA, MH, CB, TLC
Wrote the results, discussion and conclusions sections	EC, JLA, JA
Prepared the flow-chart	JLA
Prepared 'Summary of findings' tables	JLA
Made an intellectual contribution and provided the clinical perspective	EC, JLA, MH, CB, CJ, SSgB, TM, TLC, AB, JA
Edited the review	EC, JLA, MH, CB, CJ, SSgB, TM, TLC, AB, JA
Assessed MECIR standards	JLA
Approved final version of the protocol prior to submission	EC, JLA, MH, CB, CJ, SSgB, TM, TLC, AB, JA

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DECLARATIONS OF INTEREST

Agustin Benito has no known conflicts of interest.

Carmen Bouza has no known conflicts of interest.

Carolina Jimenez has no known conflicts of interest.

Estefanía Custodio has no known conflicts of interest.

Jesus Lopez Alcalde has no known conflicts of interest.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Review information

- Jesús López Alcalde is now an author, with equal contribution to Estefanía Custodio.
- New authors joined the team: CJ, TLC, SSgB, and TM.

Search methods

In the review protocol, we did not plan to contact micronutrient companies.

Assessment of risk of bias in the included studies

In the protocol, we had planned to assess risk of bias in non-randomized trials according to the Cochrane tool for non-randomized studies (ACROBAT- NRSI; (Sterne 2014)). However, this tool is now called ROBINS-I.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; *Nutrition Therapy; Leishmaniasis, Visceral [*drug therapy]; Malnutrition [*therapy]

MeSH check words

Humans