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Original article

Effectiveness of macronutrient supplementation on nutritional status and HIV/AIDS progression: A systematic review and meta-analysis

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SUMMARY

Background & aims: Malnutrition is common in Sub-Saharan Africa, weakening the immune function of persons living with HIV infection (PLWH). Being malnourished at the initiation of antiretroviral therapy (ART) leads to higher risk of early mortality and reduced quality of life. Thus, introduction of protein-energy-fortified macronutrient supplements at ART initiation may improve HIV treatment outcomes. This review aimed to evaluate the effectiveness of macronutrient interventions.

Methods: This systematic review and meta-analysis included 15 studies conducted from 2000 to 2015 among Sub-Saharan African adults.

Results: Six randomized controlled trials and 4 retrospective cohort studies provided data eligible for a meta-analysis. Supplementation significantly increased the overall standardized mean difference (SMD) between baseline and follow-up data in weight (SMD = 0.382, $p < .001$), BMI (SMD = 0.799, $p < .001$); fat-free mass (SMD = 0.154, $p = .009$); and CD4 count (SMD = 0.428, $p < .001$).

Conclusion: Protein-energy-fortified macronutrient supplementation at ART initiation may positively influence nutritional status and immunologic response in PLWH in Sub-Saharan Africa.

1. Introduction

Malnutrition—an insufficiency or unbalance of nutrition [1]—is a significant health issue in persons living with HIV (PLWH) [2,3]. In resource-limited countries, the availability of food resources to meet daily needs may not be sufficient for PLWH [4]. Since imbalanced distribution of social determinants such as socioeconomic status, local food markets, and transportation options impacts food availability [5–7], this is particularly salient in Sub-Saharan Africa where food insecurity along with many other social determinants of health [4,8,9] and co-infections such as *Mycobacterium tuberculosis* complicate the picture [10]. Malnutrition is a result of a deficiency of both macronutrients (nutrients that provide calories or energy, including carbohydrates, proteins, and fat) and micronutrients (vitamins and minerals), vital dietary components necessary for physical and mental development, disease prevention, and well-being [11,12]. Malnutrition contributes to physiological, psychological, compositional, or functional alterations [13,14].

HIV-associated wasting—involuntary weight loss greater than 10% of baseline—plus chronic diarrhea or chronic weakness are identified as acquired immunodeficiency syndrome (AIDS)-defining conditions [15]. HIV-associated wasting is specifically characterized as protein-energy malnutrition—the insufficient intake of both protein and energy—and is one of the most common conditions associated with AIDS in resource-limited settings such as Sub-Saharan Africa [16]. Protein-energy malnutrition as a cause of secondary immune deficiency accelerates susceptibility to opportunistic infections in PLWH [17,18]. Consequently, the nutritional status of the host regulates the outcome of infection, and the co-existence of HIV infection and malnutrition may lead to increased mortality [2,19–22] as well as lower quality of life (QOL) [23–25]. Therefore, correction of nutritional status for PLWH with protein-energy fortified interventions in Sub-Saharan Africa is necessary not only to reduce mortality but also to improve QOL. Nevertheless, few recommendations exist for healthcare providers to manage nutritional status for PLWH in Sub-Saharan Africa.

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Recognition of malnutrition in adults and its relation to HIV and AIDS progression as well as clinical implementation of appropriate supplementation are understudied. There is a strong need to improve nutritional status prior to initiation of antiretroviral therapy (ART); however, no clear consensus exists as to whether the introduction of protein-energy fortified macronutrient supplements with ART initiation is more effective for improving both nutritional status and immunologic response compared to ART alone. Thus, the purpose of this meta-analysis was to evaluate the effects of oral macronutrient energy-fortified nutritional interventions on nutritional and immunologic outcomes in adults living with HIV infection in Sub-Saharan Africa.

2. Materials and methods

The overall process of our systematic review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [26]. Institutional Review Board approval was not required for this review.

2.1. Data search and inclusion/exclusion criteria

PubMed, Embase, CINAHL, and Cochrane Review were searched using the terms nutritional supplements, nutrition, supplementation, nutritional support, HIV, AIDS, and Sub-Saharan Africa. Reference lists of identified articles and bibliographies of books were also reviewed. Nutritional studies involving adults with HIV/AIDS were included, while those involving pregnant women, children, and non-energy-fortified nutritional interventions (calories less than 100 kcal/day or micronutrient supplementation only) in PLWH were excluded. During the initial search, the search was not limited by year to aid in identification of classic works and was later restricted to the years from 2000 to July 2017 to provide the most current literature. Study inclusion criteria were as follows: (1) participants are HIV-infected adults age 15 years and older based on WHO classification of adults (ages 15–64 years) for an HIV epidemic and also due to higher prevalence of HIV infection among young adults (ages 15–49 years) in Sub-Saharan Africa [3], (2) our study used macronutrient supplements, (3) all study participants had the same chance to receive ART regardless of randomization, and (4) absence of comorbidities except for pulmonary mycobacterium tuberculosis (PTB). Among comorbidities, only PTB patients were accepted for review, while other comorbidities were excluded because comorbidity of PTB is the most common cause of HIV-associated death [7] as an end-stage of AIDS [15]. Even though PTB co-infection may require higher nutritional demand, modifying the effects of oral nutritional supplements on physiological outcomes, it might be impractical to exclude PTB-infected individuals from study samples of primary studies because most countries in Sub-Saharan Africa are PTB-endemic areas [7].

When duplicate reports or studies were removed, the electronic and hand search yielded 281 studies, of which 89 studies were initially screened; 41 studies then met our inclusion criteria. Through a full text review and quality assessment process for the original studies, 26 studies were dropped because of the following: (a) inadequate intervention use such as micronutrient supplementation, total parenteral nutrition, or nutritional education only; (b) non-target populations such as ART-naïve patients only, pregnant women, children, adults with other comorbidities (except for PTB or countries outside Sub-Saharan Africa); and (c) ineligible reported data for a meta-analysis such as small sample size less than 25, and studies published before 2000 (Fig. 1).

To increase confidence in the results related to the association between macronutrient intervention and outcomes and also to provide information on whether the intervention was effective [27], a meta-analysis was used where the following eligible data were utilized from randomized controlled trials (RCTs) and cohort studies: (1) baseline and follow-up mean with standard deviation (SD) or confidence intervals (CI)—6 RCTs and 4 retrospective cohort studies met this criteria; or (2) mean differences between baseline and follow-up with a type of significance values such as *p*-values or CI—2 RCTs met this criteria. Although primary studies collected data and were reported slightly differently in the published works, we utilized their summary data as mean difference, 95% confidence interval, and sample size. Thus, 12 studies were included in the meta-analysis (Table 1). We contacted 13 corresponding authors of the eligible studies with a request to provide summary data; only 1 corresponding author provided requested data, which were included in the meta-analysis. Summary statistics from eligible primary studies were abstracted by the first author and verified by the last author.

2.2. Data quality assessment

To identify the potential risk of bias of each study, the quality and rigor of the original studies were evaluated using two published quality-rating scales: the Jadad Scale [28] for RCTs and the Newcastle–Ottawa Quality Assessment Scale (NOS) [29] for cohort studies. When published literature was unrepresentative of the population of the conducted studies, a publication bias was assumed to exist [30], possibly distorting the results of data synthesis [31]. Thus, the presence of publication bias in the extracted outcomes was evaluated by Begg's test with funnel plots [32], which are a graphical plot of effect size against sample size or other indicators of the precision of the estimate such as standard error of the treatment effect or inverse variance of the treatment effect (weight) [32]. Asymmetry of the funnel plot indicates possible publication bias [32].

2.3. Data synthesis and meta-analysis

The studies included in this review were deemed comparable in relevance (research question and closeness in design) as well as for measurement of the same outcome, and were therefore pooled for a summary effect. Due to high risk of bias, studies with quality assessment scores lower than 2 out of 5 from Jadad and 4 out of 9 from NOS were not included in the meta-analysis. For these studies, only a narrative synthesis was included.

The effectiveness of intervention from 6 RCTs out of 8 were statistically measured by overall standardized mean difference (SMD or Cohen's *d*) [33]. The SMD was computed with the following formula: *SMD = {new treatment improvement − comparator (placebo) improvement}/pooled standard deviation.*

We also used 95% confidence interval for the mean difference and sample size with the *metan* command in meta-analysis by STATA 14 software [34]. The presence of heterogeneity of each trial was tested by Q statistics to choose between the fixed effect model and the random effect model and presented by I^2 index.

2.4. Descriptive analysis

2.4.1. Randomized controlled trials

Table 1 shows the study locations, type of interventions, length of interventions, and primary outcomes of the included eight RCTs. Five out of eight studies examined the effects of two different interventions by using a different type of nutritional supplements; four of the studies reported the mean differences between pre- and post-intervention in each intervention group [35–38], and one study reported the mean differences between two different intervention groups [39]. For meta-analysis, unpublished raw data of mean and SD for weight, BMI, FFM, and CD4 count before and after intervention

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