Protocol

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The effectiveness of nutritional interventions on COVID-19 outcomes: A protocol for systematic review and meta-analysis

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Abstract

Background: Despite global efforts to treat and alleviate the outcomes of COVID-19, no consensus has been reached regarding the optimal approach. Some nutrients have been known to be vital for the integrity of the immune system. Although limited interventional studies support this idea, the findings of some cross-sectional and case studies have been encouraging. **Aim:** The present study will seek to determine the effectiveness of nutritional interventions on the outcomes of COVID-19. **Methods:** Electronic databases including PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar will be searched for articles published from October 1st, 2019, to January 12th, 2022. Different study designs, both randomized and nonrandomized trials, cross-sectional or cohort studies, and pre and post-interventions will be included. Screening, selection, and extraction of data as well as quality assessment of included studies, will be carried out by two separate reviewers. Any potential conflicts will be resolved through discussion. An appropriate risk of bias assessment tool will be used to appraise the included studies. Then, the results will be synthesized and pooled for meta-analysis. If the meta-analysis is not performed, the reason will be provided. After summarizing the results and providing conclusions, the specific features associated with effective interventions will be presented based on the power of each study.

Keywords

COVID-19, nutrition, outcome, intervention

Introduction

Despite the numerous measures to combat COVID-19 disease, its global prevalence continues to rise (Baud et al., 2020). To date, no efficacious treatment for COVID-19 has been reported (Cortegiani et al., 2020). In spite of global efforts to treat and alleviate the outcomes of COVID-19, no consensus has been reached regarding the optimal approach (Siemieniuk et al., 2020).

Although the generation of COVID-19 vaccines is progressing at an unprecedented rate, the time that the vaccine takes to prepare, evaluate, produce, and distribute among people worldwide, necessitates the prevention or treatment-based methods for the disease. Therefore, ascertaining solutions that improve the functioning of the immune system has become a research priority (Nikniaz et al., 2021).

Today, there is no apparent nutritional intervention for preventing and treating SARS-CoV-2 infection. Therefore, it is necessary to carry out randomized clinical trials. Some vitamin supplements have previously been suggested to help reduce the severity of colds and acute respiratory distress syndrome and boost the immune system through their antioxidant properties. In addition, the role of vitamin and mineral supplementation has been

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investigated in some trials (Jovic et al., 2020). It has been reported that vitamin D can reduce the risk of microbial infection and death by modulating innate and consistent immunity. In addition, vitamin D has a pronounced effect on enhancing the angiotensin-converting enzyme (ACE-2) expression, an important receptor that mediates the pathogenesis of SARS-CoV-2 infection. Vitamin D can also increase the expression of genes involved in antioxidant activities, modulate adaptive immunity, and improve cellular immunity (Teshome et al., 2021). However, in some studies investigating the role of vitamin D in COVID-19, contradictory results have been observed (Ferrari and Locatelli, 2020).

Furthermore, certain indications suggest that moderation of zinc status may be beneficial in COVID-19. Laboratory studies show that zinc possesses antiviral activity by inhibiting SARS—CoV RNA polymerase. Moreover, indirect evidence also suggests that zinc may reduce the activity of the angiotensin-converting enzyme (ACE2), known as the SARS-CoV-2 receptor. Improved antiviral immunity by zinc may also occur by regulating interferon α production and increasing antiviral activity. Zinc status is also closely linked to COVID-19 risk factors such as immunodeficiency, obesity, diabetes, and atherosclerosis, as the conditions are correlated with zinc deficiency. Hence, zinc may have a protective effect as a prophylactic and adjunctive treatment of COVID-19 by reducing inflammation, improving mucociliary clearance, preventing lung damage, and modulating antiviral and antibacterial immunity (Skalny et al., 2020).

Supplementation with vitamin B may increase the oxygen index in patients infected with COVID-19, and vitamin B deficiency can significantly impair cell function and the immune system, leading to inflammation caused by hyper-homocysteinemia. Vitamin B also plays a pivotal role in cell function, energy metabolism, and proper immune function (Shakoor et al., 2021). To the best of our knowledge, although there are several significant articles on the possible role of nutrition on COVID-19 outcomes, no definitive solution in preventing or reducing coronavirus complications has yet been suggested regarding the role of nutritional factors, and in some cases contradictory results have been achieved. Therefore, in this systematic review and meta-analysis, we seek to ascertain the efficacy of nutritional interventions on the outcomes of COVID-19.

Methods

Protocol design and registration

The protocol design, search strategy, synthesis, and reporting of findings from this systematic review will be presented according to the Cochrane Collaboration Handbook of Systematic Reviews (Cumpston et al., 2019) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009b). Moreover, this systematic review protocol aligns with recommended items of Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist (Moher et al., 2015) (Additional file 1). The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42021264900.

Inclusion criteria

Types of studies. The authors will review all studies related to nutritional interventions on COVID-19 outcomes published between October 1st, 2019 to January 12th, 2022. Therefore, the systematic review will include different study designs, both randomized and non-randomized trials, cross-sectional or cohort studies, and pre and post-interventions. The search will be performed using the following keywords: quarant*, lockdown*, covid*, coronav*, pandem*, food*, diet*, feed*, supplement*, vitamin*, micronut*, macronut*, eat*, vegetab*, fruit*, interven*, trial*, and ethic*. In the primary search we identified 2780 articles through database searches.

Types of participants. All adult hospitalized patients who have a laboratory-confirmed diagnosis of COVID-19, will be evaluated.

Types of comparison/exposure. In this systematic review, all nutritional interventions, such as nutritional supplementations, dietary advice, and counseling, will be evaluated as factors affecting the clinical outcomes and prognosis of COVID -19 disease.

Types of outcome measures. The primary outcome will be the prevention and/or control of COVID-19, including; duration of hospitalization, need for ICU admission, disease progression, and survival.

The proportion of anxiety or depression, morbidity, and other adverse outcomes, including the proportion of overweight or obesity, will be included in post-covid-19 morbidity as secondary outcomes.

Exclusion criteria

Inappropriate study design (qualitative, review articles, letters, commentaries or case reports and case series with COVID-19 patients), observational studies evaluating risk factors for adverse clinical outcomes in patients infected by COVID, studies that examined nutritional interventions in other coronaviruses, and non-English articles will be excluded.

Search strategy

Electronic databases including PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar will be searched for articles published from October 1st, 2019 to January 12th, 2022. In addition, clinical trial registries, including Clinicaltrial.gov, will be searched for ongoing trials. Further, we will search grey literature (e.g. thesis or dissertations, conference papers, and final reports of research projects) in Google Scholar and ProQuest for related theses/dissertations, SCOPUS, and Web of Science for conference papers.

For the database searches, we will use the suggested query or the strategy suited to the environment of the database to search the studies. The search strategy for MEDLINE/PubMed, according to PICO format and the MeSH database, can be found in Supplementary File 1. In order to find other potentially relevant articles, we will also search the reference lists of the included studies. If any systematic reviews are identified, we will hand search their list of references for relevant studies to include.

Screening and selection processes

All search results will be imported to Endnote reference manager software for de-duplicating and further evaluation. Then, two reviewers independently will screen the remaining studies for eligibility by their titles and abstracts. Any conflicts will be resolved by discussion with a third reviewer. A full-text screening will be carried out according to inclusion and exclusion criteria by two independent reviewers. The reasons for the exclusion of the full-text article will be documented. The PRISMA flowchart (Moher et al., 2009a) will depict the selection process.

Data extraction

Data extraction will be performed using an initially-pilot-tested standardized form, including study title, author(s), publication year, geographic origin, study design, population characteristics (sample size, age, gender, ethnicity, and the country the intervention was conducted in), primary and secondary outcomes, and effect size.

Assessment of risk of bias in included studies

Two reviewers will independently assess the risk of bias, including selection bias, performance bias, detection bias, attrition bias, and reporting bias, by assigning a rating of low, high or unclear risk of bias. Quality assessment of included studies will be evaluated using the Newcastle-Ottawa quality assessment scale (NOS) (Wells et al., 2017). A score greater than seven stars out of nine (total score) will be considered high quality. The data extraction and quality assessment will be performed independently by two reviewers then will be checked by a third reviewer. Disagreements will be resolved by discussion. The overall strength of the evidence will be illustrated in a risk of bias graph. Forest plots will provide depictions of the overall effect. In addition, effect sizes will also be calculated for each individual study.

Measures of intervention effect

We will perform meta-analyzes to compute the odds ratio (OR) and 95% CI of different nutritional interventions in COVID-19 patients with or without severe illness and non-survivors or survivors. Adjusted effect estimates for age, gender, ethnicity, body mass index, and other potential confounders will be presented. Moreover, we will also include studies that reported either the median and IQR or the mean and standard deviation (e.g. number of hospitalization days) in meta-analyzes. If the meta-analysis is not performed, the reason will be provided, and after summarizing the results and providing conclusions, the specific features associated with effective interventions will be presented based on the power of each study.

Assessment of heterogeneity

Heterogeneity will be assessed using a Chi-square test, with an alpha of 0.05 (for statistical significance) and the I^2 test (Milner, 2003), with I^2 values of 25%, 50%, and 75% corresponding to low, medium, and high levels of heterogeneity, respectively.

Assessment of publication bias

Publication bias will be investigated using funnel plots, Egger's test (Egger et al., 1997), and Begg's test (Begg and Mazumdar, 1994), and the results will be considered to indicate potential minor study effects when P values are <0.10.

Data synthesis

The meta-analyzes will be performed using the inverse variance method with the random-effects model. We will perform a regression-based Harbord's test for dichotomous outcomes to assess the small-study effect. All analyzes will be conducted using STATA (13.0; Stata Corporation, College Station, Texas, USA Stata), and the statistical significance level will be set, *a priori*, at $P < 0.05$.

Additional analyzes

We will conduct a subgroup analysis for each outcome (not infected by the disease, duration of hospitalization, need for ICU admission, disease progression, and survival). Sensitivity analyzes will be conducted by excluding studies with a sample size of less than 100. Random-effects meta-regression will be performed using a restricted-maximum likelihood for pre-specified variables including age, gender, comorbidity diseases such as hypertension, diabetes mellitus, and cardiovascular disease.

Summary

Although some research has been published pertaining to the possible role of nutrition on COVID-19 outcomes, to the best of our knowledge, no definitive solution in preventing or reducing coronavirus complications has yet been suggested regarding the role of nutritional factors. In the extant literature, contradictory results have been reported. Therefore, in this systematic review and meta-analysis, we seek to ascertain the efficacy of nutritional interventions on the outcomes of COVID-19. Adequate nutrition is known to be essential for the proper function of the cells in the immune system, and some nutrients, including essential amino acids, vitamins, and minerals, are vital for the integrity of the immune system (Cámara et al., 2021; Childs et al., 2019). Although relatively few interventional studies support the notion that nutritional supplementation may alleviate coronavirus complications, the findings of some cross-sectional and case-control studies have been encouraging. A study in Mexico reported that Vitamin D-deficient patients were almost four times more likely to die from COVID-19 (Pérez et al., 2020). In addition, a cross-sectional study indicated that 76% and 42% of the patients with COVID-19 lacked vitamin D and selenium, respectively (Im et al., 2020). Given that proper nutrient intake may boost the immune system to fight against coronavirus, nutrient supplementations may represent an efficient strategy to suppress the adverse effects of COVID-19.

Limitations

Nonrandomized interventions are subject to more bias compared to randomized studies; however, due to the scarcity of papers describing randomized interventions on COVID-19, the current study will also assess data from nonrandomized studies.

List of abbreviations

ACE-2	angiotensin-converting enzyme
CI	Confidence Interval
COVID-19	coronavirus disease 2019
ICU	Intensive Care Unit
IQR	Interquartile Range
MeSH	Medical Subject Heading
NOS	Newcastle-Ottawa quality assessment scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO	Prospective Register of Systematic Reviews

Authors' contributions

MA, AD and CC contributed to conception and design. MA and AD contributed to acquisition of data. MA and AD drafted the article. CC critically revised the article for intellectual content. AD, MA and CC approved the final version to be published

Ethical approval

The responsible investigator will ensure that this study is conducted in agreement with both the Declaration of Helsinki and the laws and regulations of the country.

Consent for publication

Not applicable

Availability of data and materials

Anonymized data generated during the study will be made available by the corresponding author on request.

Declaration of conflicting interests

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Supplemental Material

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