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Original Article

ORIGINAL ARTICLE

Effects of oral nutritional supplements on the nutritional status and inflammatory markers in patients on maintenance dialysis: a systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Background and aims. Patients on hemodialysis (HD) or peritoneal dialysis (PD) often have insufficient energy and protein intake, resulting in poor nutritional status and adverse outcomes. Oral nutritional supplements (ONSs) are the most commonly used to increase such patients' energy and protein intakes.

Methods. In this systematic review and meta-analysis, we analyzed studies on nutritional status, inflammatory markers, and electrolyte levels in patients on dialysis receiving ONSs. We searched four electronic databases from inception until 31 December 2022, for randomized controlled trials comparing ONS treatment versus placebo or routine care.

Results. 22 studies with 1185 patients on dialysis were included in our meta-analysis. Compared with the control group, the ONS group exhibited significantly increased serum albumin levels [1.26 g/l (95%CI, 0.50–2.02, $P < 0.0001$; $I^2 = 80.4\%$)], body mass indexes (BMIs) [0.30 kg/m^2 (95%CI, 0.09–0.52, $P = 0.005$; $I^2 = 41.4\%$)], and handgrip strength (HGS) [0.96 kg (95%CI, 0.07–1.84, $P = 0.034$; $I^2 = 41.4\%$)] from baseline to the end of intervention. No significant differences were observed between the groups in lean body mass, phase angle, C-reactive protein, and serum phosphorus and potassium levels. In terms of improving albumin, the subgroup analyses show that ONS use seems to be more inclined to three variations: HD patients, short-term use, and non-intradialytic supplementation.

Conclusion. In conclusion, ONS use can improve the nutritional status of patients on dialysis in terms of their serum albumin, BMI, and HGS without significant effects on serum phosphorus, potassium, and C-reactive protein levels. However, it remains uncertain whether these results translate to improvement in clinically relevant outcomes. Large-scale high-quality studies are still required in this population.

LAY SUMMARY

Patients on hemodialysis (HD) or peritoneal dialysis (PD) often have insufficient energy and protein intake, resulting in poor nutritional status and adverse outcomes. Oral nutritional supplements (ONSs) are the most commonly used to increase such patients' energy and protein intakes. In this systematic review and meta-analysis, we analyzed studies on nutritional status, inflammatory markers, and electrolyte levels in patients on dialysis receiving ONSs. We searched four electronic databases from inception until 31 December 2022, for randomized controlled trials

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comparing ONS treatment versus placebo or routine care. We included 22 studies with 1185 patients on dialysis in our meta-analysis. Compared with the control group, the ONS group exhibited significantly increased serum albumin levels, body mass indexes (BMIs), and handgrip strength (HGS) from baseline to the end of intervention. No significant differences were observed between the groups in lean body mass, phase angle, C-reactive protein, and serum phosphorus and potassium levels. In conclusion, ONS use can improve the nutritional status of patients on dialysis in terms of their serum albumin, BMI, and HGS without significant effects on serum phosphorus, potassium, and C-reactive protein levels. However, the quality of the evidence remains low, and large-scale high-quality studies are required to verify our findings.

Keywords: albumin, chronic kidney disease, hemodialysis, nutritional status, oral nutritional supplements, peritoneal dialysis

INTRODUCTION

Hemodialysis (HD) and peritoneal dialysis (PD) are the two common forms of dialysis therapy for end-stage renal disease. Metabolic waste that is typically produced by food intake can be depurated by dialysis. Patients with chronic kidney disease (CKD) undergoing HD or PD are often prescribed dietary restrictions—in particular, restrictions involving foods rich in sodium, potassium, and phosphorus. In addition, the intake of energy and/or protein in dialysis patients is often reduced due to gastrointestinal symptoms such as nausea or anorexia. Thus, patients on dialysis commonly develop malnutrition and protein-energy wasting (PEW) [1–3]. PEW, a state of multiple metabolic and nutritional abnormalities resulting from a combination of insufficient intake, metabolic acidosis, uremic toxins, inflammation, and hypercatabolism [4] also causes poor quality of life and increases the risk of adverse outcomes [5]. Given the influence of such energy wasting on patients with CKD or those undergoing dialysis, the International Society of Renal Nutrition and Metabolism introduced the term PEW in 2008 to describe the state of decreased body stores of protein and energy.

The latest Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (2020) state that adequate protein and energy intake in the regular diet is critical for patients on HD and PD [6]. However, the energy and protein intake from regular meals is generally lower than that of the recommended amount for these patients [7–9]. This low intake is a critical factor in the etiology of PEW in patients with CKD, especially those undergoing maintenance dialysis therapy (MDT) [7, 8]. Consequently, considerable research effort has been directed toward developing effective strategies for maintaining or improving the nutritional status of patients on dialysis, with the most common approach being providing food and nutritional supplements [10].

Several observational studies have indicated that consuming oral nutritional supplements (ONSs) or extra snacks improves nutritional status in terms of albumin or anthropometric measures in patients on dialysis [11–14]. Moreover, some studies have reported that ONS use is associated with improved outcomes in patients on HD [15–18]. In dialysis patients where oral dietary intake from regular meals cannot maintain adequate nutritional status, nutritional supplementation, administered orally, enterally, or parenterally, is shown to be effective in replenishing protein and energy stores [19]. In clinical practice, the ONS use is the preferred pathway. However, many problems related to this practice, such as postprandial hypotension, gastrointestinal symptoms, and reduced treatment efficiency, have led to the favorability of its implementation being debated and to inconsistencies in the policies related to in-center nutrition within dialysis clinics [20, 21]. Therefore, randomized controlled trials (RCTs) are required to clarify the risk–benefit profile of ONS use in patients on dialysis and to determine whether ONS use can improve the prognosis of these patients by improving their nutritional status.

No consensus exists on the type, time of initiation, or duration of use of enteral nutrition or nutritional supplementation for patients on MDT. Although our previous meta-analysis of this topic [22] included many RCTs [23–38], most had a small sample size and were of low quality. Moreover, considerable heterogeneity was noted among these studies. These factors led to a very low level of evidence for ONS use improving the nutritional status of patients on dialysis [22]. Similarly, a recent meta-analysis concluded that protein-based ONS use can effectively improve the nutritional status in terms of serum albumin in patients with CKD requiring dialysis, albeit with high heterogeneity among the included studies [39]. Six relevant RCTs have been published [40–45] since our previous meta-analysis [22], and one had a large sample size ($N = 240$) [42]. Therefore, we conducted an updated systematic review and meta-analysis of RCTs to further quantitatively evaluate the effect of ONS use versus routine or placebo care on patients on dialysis.

MATERIALS AND METHODS

Search strategy

The present meta-analysis was conducted and reported on the basis of the PRISMA guidelines [46]. We searched the PubMed, Embase, ClinicalTrials.gov, and Cochrane Library databases for eligible studies from inception to 31 December 2022 (all databases were retrieved using 'age >18 years' as a filter). Studies investigating the association between ONS use and the nutritional status, with the studies' data including those on serum albumin levels, body mass index (BMI), lean body mass, handgrip strength (HGS), electrolyte levels, and inflammation levels, of adult patients on dialysis were retrieved using the following search terms: dialysis, hemodialysis, haemodialysis, hemofiltration, peritoneal dialysis, renal replacement therapy, chronic renal failure, end-stage renal disease, chronic kidney disease, CKD, nutrition supplement*, nutritional support, oral nutritional supplement, ONS, oral supplement*, nutrient*, macronutrients, calorie supplement*, energy supplement*, protein supplement*, and amino acid supplement*. The complete search strategy is presented in Supplementary Table S1. In addition, we manually

Table 1: Summary of inclusion and exclusion criteria applied during evaluation of studies for review.

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Adults studies (age ≥18 years) Nutrition status (either well nourished or malnourished) Patients on dialysis (of any type)	Animal data Dialysis patients with HIV infection or acute infection
Intervention	All studies using oral nutritional supplements with any macronutrient (carbohydrate, fat, or protein/amino acid) Setting in hospital or community (outpatient or home)	Feeds only given non-caloric nutrients or Beta-hydroxy beta-methylbutyrate (HMB) or concomitantly given keto acid or keto analogs
Comparison	Placebo, routine care, or no supplementation	Without control group
Outcome measures	Serum albumin level; BMIs; fat-free mass or lean body mass; handgrip strength; phase angle; Electrolytes (serum potassium and phosphate); C-reactive protein	Studies without any predetermined outcome measure
Study type	Randomized controlled trials	Non-randomized studies

searched the reference lists of the retrieved articles for other potentially relevant studies.

Inclusion and exclusion criteria

We selected RCTs in which patients on dialysis (HD or PD) were administered ONSs as the intervention. The other inclusion criteria were as follows: (i) included a comparison of the effects of oral non-protein (carbohydrates or fat/lipids) or protein/amino acid or energy-based mixed nutritional supplements with or without micronutrients with those of standard care with or without placebo care; (ii) reported at least one of the following: BMI, lean body mass (measured using dual-energy X-ray absorptiometry or bioelectrical impedance), HGS, phase angle, serum albumin levels, phosphorus level, potassium level, and C-reactive protein (CRP) level; (iii) used a commercial or a noncommercial ONS that provided calories; and (iv) included only patients older than 18 years. The details are presented in Table 1.

We excluded RCTs that did not report mean [standard deviation (SD)] changes in BMI, lean body mass, HGS, phase angle, serum albumin levels, phosphorus levels, potassium levels, and CRP for the intervention and control groups. In addition, abstracts without full articles, reviews, and case reports were excluded.

Data extraction

Two independent reviewers (L.P.J. and G.J.Y.) extracted data from the full texts of the eligible studies. Disagreements were resolved through discussion with a third reviewer (Y.K.). The following data were extracted: the name of the first author, publication year, sample size of each comparison group, duration of interventions, study population, intervention modality in case and control groups, and participant characteristics (BMI, lean body mass, HGS, phase angle, serum albumin levels, phosphorus levels, potassium levels, and CRP before and after the intervention). If the trial was a crossover study, the outcomes at the end of the first phase (before the crossover) were analyzed.

Data synthesis and statistical analysis

The changes in each outcome were reported as differences between mean values before and after the intervention. If the means and SDs of the changes from baseline were specified in the papers, they were directly used. If not, the mean changes in the observed parameters were calculated by subtracting the baseline values from the values after the intervention, and the SD of the difference was calculated as follows [47]:

$$SD = \sqrt{SD1 * SD1 + SD2 * SD2 - 2R * SD1 * SD2}\ (R = 0.5)$$

If a two-arm design was used to implement interventions of the same nature, the two arms were merged using the following method [22]:

$$N_{merged} = N_1 + N_2;\ Mean_{merged} = \frac{Mean1 * N1 + Mean2 * N2}{N1 + N2}$$

$$SD_{merged} = \sqrt{\frac{(N1-1) * SD1 * SD1 + (N2-1) * SD2 * SD2 + \frac{N1*N2}{N1+N2}(Mean1 - Mean2) * (Mean1 - Mean2)}{N1 + N2 - 1}}$$

Meta-analysis was performed using STATA v.12.0 (Stata, College Station, TX, USA) and Review Manager v.5.3 (Cochrane Collaboration). The effects of the intervention are presented as mean differences (MDs) or standardized MDs, when appropriate. The heterogeneity between studies was evaluated using the I^2 index. If $I^2 > 0\%$, a random-effects model was used, and subgroup analysis was further required to identify the source of the heterogeneity. If not, the fixed-effects model was applied. Statistical significance was defined as two-tailed $P < 0.05$. Publication bias was assessed using funnel plots and the Egger test.

RESULTS

Study characteristics

Figure 1 illustrates the flowchart of the study selection. The initial search yielded 15 338 entries. After removing duplicate entries and excluding irrelevant studies through title and abstract review, we retrieved the full texts of 66 studies for evaluation. Finally, 22 studies were included in the meta-analysis [23–38, 40–45]. The characteristics of the included studies are summarized in Table 2.

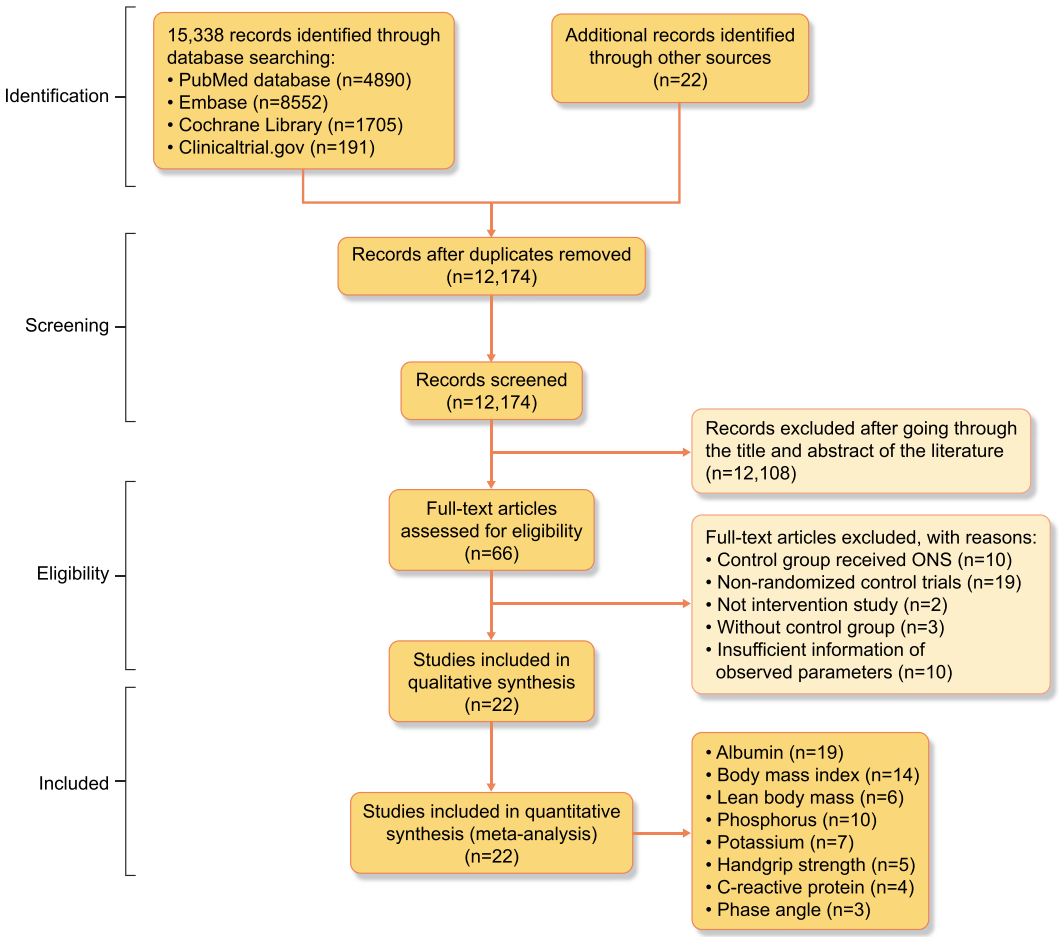

Figure 1: Flowchart of study selection.

Quality assessment and risk of bias findings

A quality assessment of the included studies was performed with reference to the *Cochrane Handbook for Systematic Reviews of Interventions* (Fig. 2A and B). The risk of bias assessment involved the following domains: random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, blinding of the outcome assessment, incomplete outcome data, selective outcome reporting, and other bias.

Overall effects of ONS use on serum albumin levels

The overall effects of ONS use on serum albumin levels are presented in Fig. 3. Nineteen trials reported changes in serum albumin levels before and after the intervention. Serum albumin levels significantly increased by 1.26 g/l (95% CI: 0.50–2.02, $P = 0.001$) in the ONS groups compared with the control groups. A significant degree of heterogeneity was observed ($I^2 = 80.4\%$, $P < 0.001$). Subsequently, a subgroup analysis was performed.

Subgroup analysis of ONS use on serum albumin levels

Subgroup analyses were conducted on suspected variables, including the type of dialysis, intervention duration, supplementation timing, nutritional status, and type of ONS. The results are presented in Table 3.

On the basis of the type of dialysis, the patients were divided into an HD group [23–25, 31–33, 36–38, 40–44] and a PD group [26, 29, 34, 35, 37]. The results revealed that ONS use significantly increased the serum albumin levels in patients on HD (1.51 g/l, 95% CI: 0.65–2.37, $I^2 = 84.6\%$, $P = 0.001$) but not in patients on PD.

On the basis of their intervention durations, the included studies were divided into a long-term intervention group (≥6 months) [23, 29, 30, 34–36, 40, 43, 44] and a short-term intervention group (<6 months) [24–26, 31–33, 37, 38, 41, 42]. This subgroup analysis indicated that short-term ONS use increased serum albumin levels (2.32 g/l, 95% CI: 1.38–3.27, $I^2 = 73.4\%$, $P < 0.001$) but long-term ONS use did not.

When the included studies were divided into intradialytic [23, 24, 31, 33, 40] and non-intradialytic [25, 26, 29, 30, 32, 34–38, 41–44] ONS groups on the basis of their supplementation timing, we observed that ONS significantly increased serum albumin levels in the non-intradialytic group (1.21 g/l, 95% CI: 0.21–2.21, $I^2 = 78.4\%$, $P < 0.018$) but not in the intradialytic group.

Other subgroup analyses indicated that ONS improved serum albumin levels in patients on dialysis with malnourished [24, 29, 31, 32, 35, 38, 41, 43] or unspecified malnourished status [23, 25, 26, 30, 33, 34, 36, 37, 40, 42, 44] and in those who were given protein/amino acid [23, 25, 26, 29–31, 33, 35, 37, 40, 44] or non-protein or mixed ONSs [24, 32, 34, 36, 38, 41–43].

Table 2: Characteristics of the studies included in the meta-analysis.

Reference (published year)	Patients (*n*) in each group	Population description	Intervention modality of case group	Intervention modality of control group	Study design and duration	Main outcomes measures in analysis
Tomayko EJ *et al.* (2015) [23]	Case (11 and 12); control (15)	MHD patients, treatment for ≥3 months, ≥3 days/week, nutritional status was not stated	27 g whey or 27 soy protein within beverage, consumed within 15 mins of dialysis; intradialytic supplementation	2 g non-caloric powder within beverage, consumed within 15 mins of dialysis	Randomized, controlled, blinded; 6 mo	Albumin, phosphorus, and potassium
Calegari A *et al.* (2011) [24]	Case (9); control (6)	Malnourished HD patients (SGA > 15 points)	Non-industrialized nutrition supplement (Thick mixed food), 355 kcal, 53% of carbohydrate, 10 g of protein, and 15 g of lipid; intradialytic supplementation	Routine nutritional guidance	Randomized, controlled, non-blinded, crossover; 3 mo (first phase)	BMI, LBM, albumin, phosphorus, and potassium
Bolasco P *et al.* (2011) [25]	Case (15); control (14)	HD patients, thrice-weekly albumin <3.5 g/dl and BMI > 20 kg/m^2, nutritional status was not stated	12 g amino acid powder dissolved in water; non-intradialytic supplementation	No intervention	Randomized, controlled, non-blinded;3 mo	BMI, phase angle, LBM, albumin, and CRP
Tabibi H *et al.* (2010) [26]	Case (18); control (18)	Continuous ambulatory PD; nutritional status was not stated	28 g packets of raw textured soy flour (containing 14 g of soy protein); non-intradialytic supplementation	Usual diet without consumption of soy-containing products	Randomized, controlled, non-blinded;8 weeks	Albumin
Imani H *et al.* (2009) [27]	Case (18); control (18)	Continuous ambulatory PD; nutritional status was not stated	28 g packets of raw textured soy flour (containing 14 g of soy protein); non-intradialytic supplementation	Usual diet without consumption of soy-containing products	Randomized, controlled, non-blinded;8 weeks	Phosphorus
Fouque D *et al.* (2008) [28]	Case (37); control (29)	MHD patients, albumin <40 g/l and BMI <30 kg/m^2; mildly nourished	250 ml Renilon 7.5 daily, 500 kcal, containing 18.75 g protein and 15 mg phosphotus; non-intradialytic supplementation	Standard care	Multicenter, randomized, open-label, controlled; 3 mo	BMI
González-Espinoza L *et al.* (2005) [29]	Case (13); control (15)	Continuous ambulatory PD for at least 1 month; malnourished	22 g of high biological-value protein (egg albumin) daily; non-intradialytic supplementation	Conventional nutritional counseling	Randomized, open-label, controlled; 6 mo	Albumin, phosphorus, and potassium
Morretti HD *et al.* (2009) [30]	Case (31); Control (18)	HD and PD patients; nutritional status was not stated	15 g liquid hydrolyzed collagen protein (3 times per week for HD patients and 7 times per week for PD patients); non-intradialytic supplementation	No supplement	Randomized,controlled, non-blinded, crossover; 6 mo	Albumin
Sohrabi Z *et al.* (2016) [31]	Case (23): control (23)	Regular HD patients with malnutrition	15 g whey protein without vitamin E (three times per week); intradialytic supplementation	No intervention	Randomized, controlled, non-blinded;8 weeks	BMI, LBM, albumin, and phosphorus

Table 2: Continued

Reference (published year)	Patients (*n*) in each group	Population description	Intervention modality of case group	Intervention modality of control group	Study design and duration	Main outcomes measures in analysis
Hung SC *et al.* (2009) [32]	Case (20); control (21)	Nondiabetic HD patients; malnourished	Daily use of one can of a commercially ONS (475 kcal, contained 16.6 g protein, 22.7 g fat, and 52.8 g carbohydrate); non-intradialytic supplementation	Without supplementation	Prospective, randomized, controlled, non-blinded; 12 weeks	BMI and albumin
Rattanasompattikul M *et al.* (2013) [33]	Case (22); Control (21)	MHD patients with Alb <40 g/l; nutritional status was not stated	19 g protein combined with fish oil, borage oil, beta-carotene, vitamin C and E, zinc, and selenium; intradialytic supplementation	Placebo	Randomized, double-blind, controlled; 16 weeks	Albumin, CRP, phosphorus, and potassium
Teixidó-Planas J *et al.* (2005) [34]	Case (35); control (30)	PD patients; nutritional status was not stated	200 ml (200 kcal) of an oral supplement with mixed nutrients; non-intradialytic supplementation	Standard care	randomized, open-label, controlled; 12 mo	Albumin and LBM
Sahathevan S, *et al.* (2018) [35]	Case (37); control (37)	Malnourished PD patients, with Alb <40 g/l and BMI < 24.0 kg/m^2	27.4 g whey protein powder ingested post-meal plus dietary counseling; non-intradialytic supplementation	dietary counseling only	Randomized, controlled, open-label 6 mo	Albumin, HGS, BMI, LBM, and phosphorus
Allman MA *et al.* (1990) [36]	Case (9)/Control (12)	Regular HD patients for >3 months; nutritional status was not stated	100–150 g glucose-polymer (400–600 kcal) plus water-soluble vitamin; non-intradialytic supplementation	No energy supplement	Randomized controlled, non-blinded;6 mo	BMI, LBM, and albumin
Eustace JA *et al.* (2000) [37]	HD: Case (14); control (15) PD: Case (9); Control (9)	HD and PD patients, albumin <3.8 g/dl); nutritional status was not stated	Daily 10.8 g EAA with meals; non-intradialytic supplementation	Placebo in appearance to the EAA tablets	Randomized, double-blind, controlled; 3 mo	BMI, HGS and albumin
Sharma M *et al.* (2002) [38]	Case (16 and 10); control (14)	Malnourished; regular thrice-weekly MHD patients (for at least 1 month) and BMI <20 kg/m^2 and albumin <4.0 g/dL	Standard home-prepared ONS: (500 kcal and 15 g protein) versus CKD-specific ONS (Reno care II, Criticare, Mumbai, India: 500 kcal and 15 g protein); non-intradialytic supplementation	Dietary counseling no specific post-HD supplement	Randomized, controlled, non-blinded;1 mo	BMI, albumin, potassium and phosphorus
Jeong JH, *et al.* (2019) [40]	Case (45); control (44)	Regular HD patients for ≥3 months; nutritional status was not stated	30 g whey protein mixed in 4–6 ounces of water; intradialytic supplementation	~150 g of a non-nutritive beverage during dialysis session	Randomized controlled, non-blinded; 12 mo	BMI, LBM, CRP, and albumin

Table 2: Continued

Reference (published year)	Patients (*n*) in each group	Population description	Intervention modality of case group	Intervention modality of control group	Study design and duration	Main outcomes measures in analysis
Limwannata P *et al.* (2021) [41]	Case A (28); case B (30); control (28)	Regular HD patients for ≥3 months; Malnourished HD patients (Alb <38 g/l and energy intake <25 kcal/kg/day and protein intake <1 g/kg/day)	Case A: 370 kcal sachets of NEPRO (16.63 g whey protein, 33 g carbohydrate, and 19.76 g fat); Case B: 370 kcal sachets of ONCE dialyze (16.98 g whey protein, 41.19 g carbohydrate, and 16.45 g fat); non-intradialytic supplementation	Diet counseling without supplements	Randomized, non-blind, controlled; 30 days	BMI, HGS, albumin, phosphorus, and potassium
Yang Y *et al.* (2021) [42]	Case (120); Control (120)	Regular HD patients for >3 months; nutritional status was not stated	60 ml (300 kcal) of an oral supplement once per day, and fat provides 97% of the total energy; non-intradialytic supplementation	Usual diet without supplements	Randomized, non-blind, controlled; 12 weeks	BMI, phase angle, HGS, and albumin
Wen L *et al.* (2022) [43]	Case (52); control (52)	Regular HD patients for >3 months; malnourished(7-point SGA ≤ 5)	Non-protein calorie jelly, each serving contained 5.4 g of fat and 22.5 g of carbohydrate, twice a day; non-intradialytic supplementation	Usual diet without supplements	Randomized controlled, non-blinded; 6 mo	BMI, HGS, albumin, and phosphorus
Murtas S *et al.* (2022) [44]	Case (11); Control (11)	Regular HD patients for >3 months; nutritional status was not stated	Sachets of amino acid mixture. A total of 31.5 g of amino acids were given weekly; non-intradialytic supplementation	Sachets of placebo	Randomized, double-blind, controlled; 6 mo	phase angle, Albumin, BMI, phosphorus, CRP, and potassium
Qin A *et al.* (2022) [45]	Case (20); Control (21)	Regular HD patients for ≥3 months; patients with PEW	30 ml of an ONS, twice a day (supplied 300 kcal per day; 2.0 g of carbohydrates, and 26.9 g of lipids); non-intradialytic supplementation	dietary recommendations without supplements	Randomized, non-blind, controlled; two mo	Phosphorus

MHD, maintenance hemodialysis; HD, hemodialysis; PD, peritoneal dialysis; HGS, handgrip strength; LBM, lean body mass; SGA, subjective global assessment; PEW, protein-energy wasting; ONS, oral nutritional supplement.

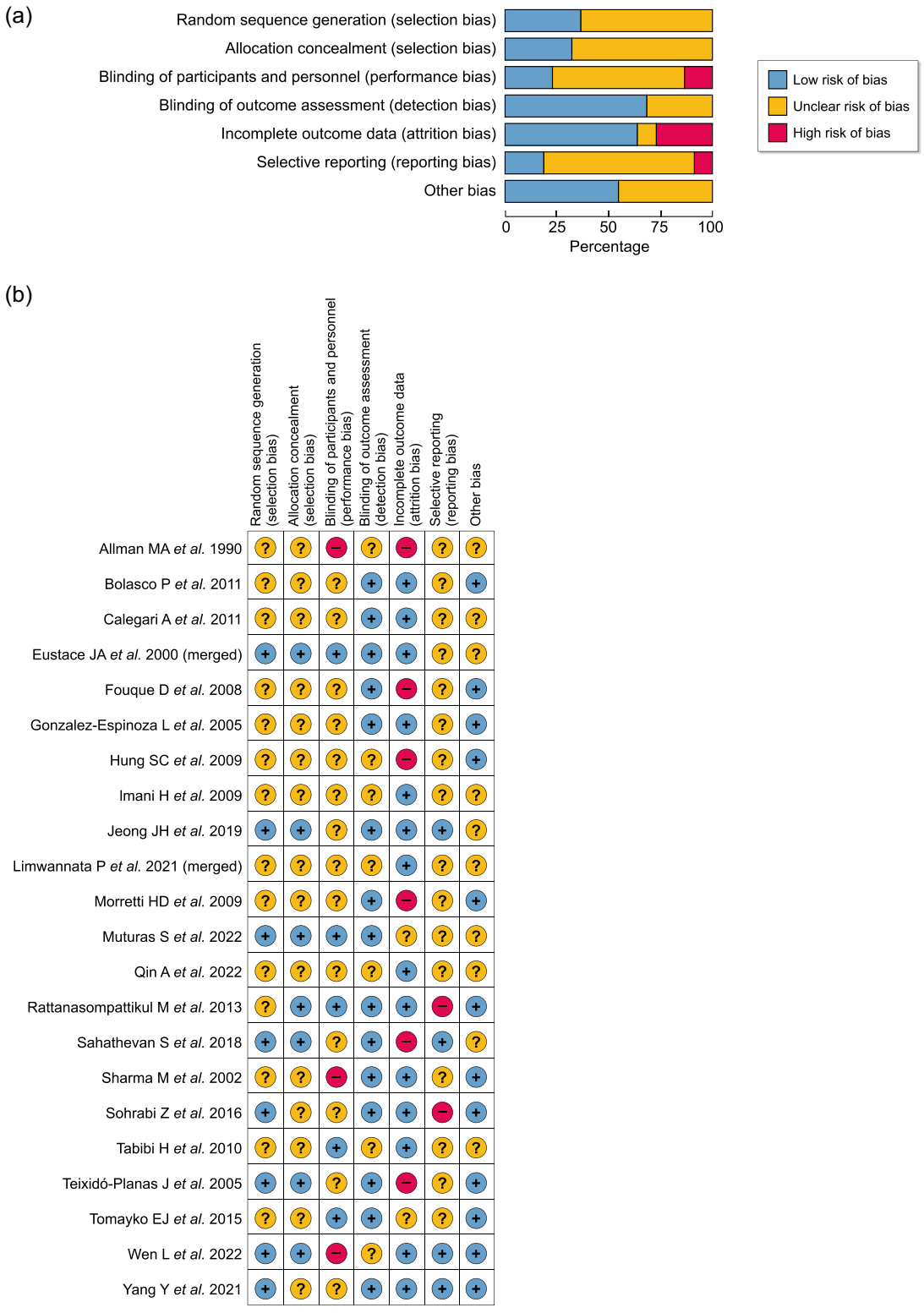

Figure 2: (a) Risk of bias in seven domains for all included studies. (b) Risk of bias assessment across seven domains for each included study.

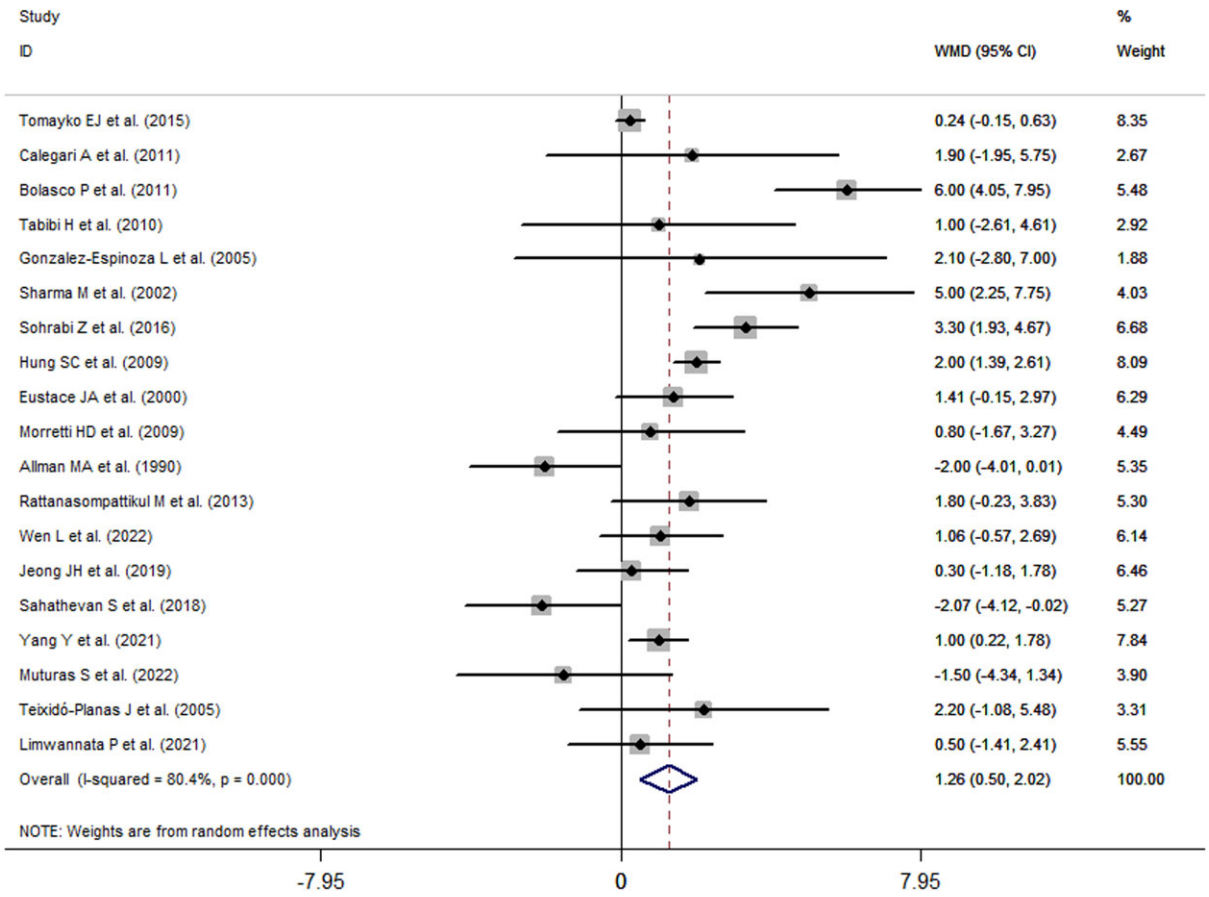

Figure 3: Forest plots depicting the overall effect of ONS use on serum albumin levels.

Table 3: Results of subgroup analyses of the effects of ONS use on serum albumin levels.

		Serum albumin (g/l)			
Subgroup		Effect size	95% CI	I^2	*P* value
Type of dialysis	Hemodialysis ($n = 14$)	1.51	0.65, 2.37	84.6%	0.001
	PD ($n = 5$)	0.21	−1.58, 2.01	39.4%	0.815
Intervention duration	<6 months ($n = 10$)	2.32	1.38, 3.27	73.4%	<0.0001
	≥6 months ($n = 9$)	−0.03	−0.82, 0.76	42.9%	0.939
Supplementation timing	Intradialytic ($n = 5$)	1.38	−0.03, 2.79	79.8%	0.055
	Not intradialytic ($n = 14$)	1.21	0.21, 2.21	78.4%	0.018
Nutritional status	malnourished ($n = 8$)	1.63	0.39, 2.88	73.5%	0.01
	Malnourishment not specified ($n = 11$)	1.01	0.05, 1.96	78.2%	0.039
Type of ONS	Protein/amino acid ($n = 11$)	1.24	0.02, 2.45	83.1%	0.046
	Non-protein or mixed ($n = 8$)	1.26	0.25, 2.27	70.2%	0.014

ONS, oral nutritional supplements; CI, confidence interval.

Effects of ONS use on BMI and lean body mass

The effects of ONS use on the BMIs and lean body masses of patients on dialysis are presented in Fig. 4A and B. Of the included studies, 14 and 7 trials reported results related to or changes in BMI and lean body mass, respectively. When statistically pooled, the changes in BMI and lean body mass were 0.30 kg/m^2 (95% CI: 0.09 to 0.52, $I^2 = 41.4\%$, $P = 0.005$), and 0.11 kg (95% CI: −1.20 to 1.43, $I^2 = 51\%$, $P = 0.868$), respectively, indicating that ONS use significantly increased the BMI but not lean body mass of patients on MDT.

Effects of ONS use on handgrip strength and phase angle

Five studies reported changes in HGS, and three studies described changes in phase angle, respectively. The pooled data

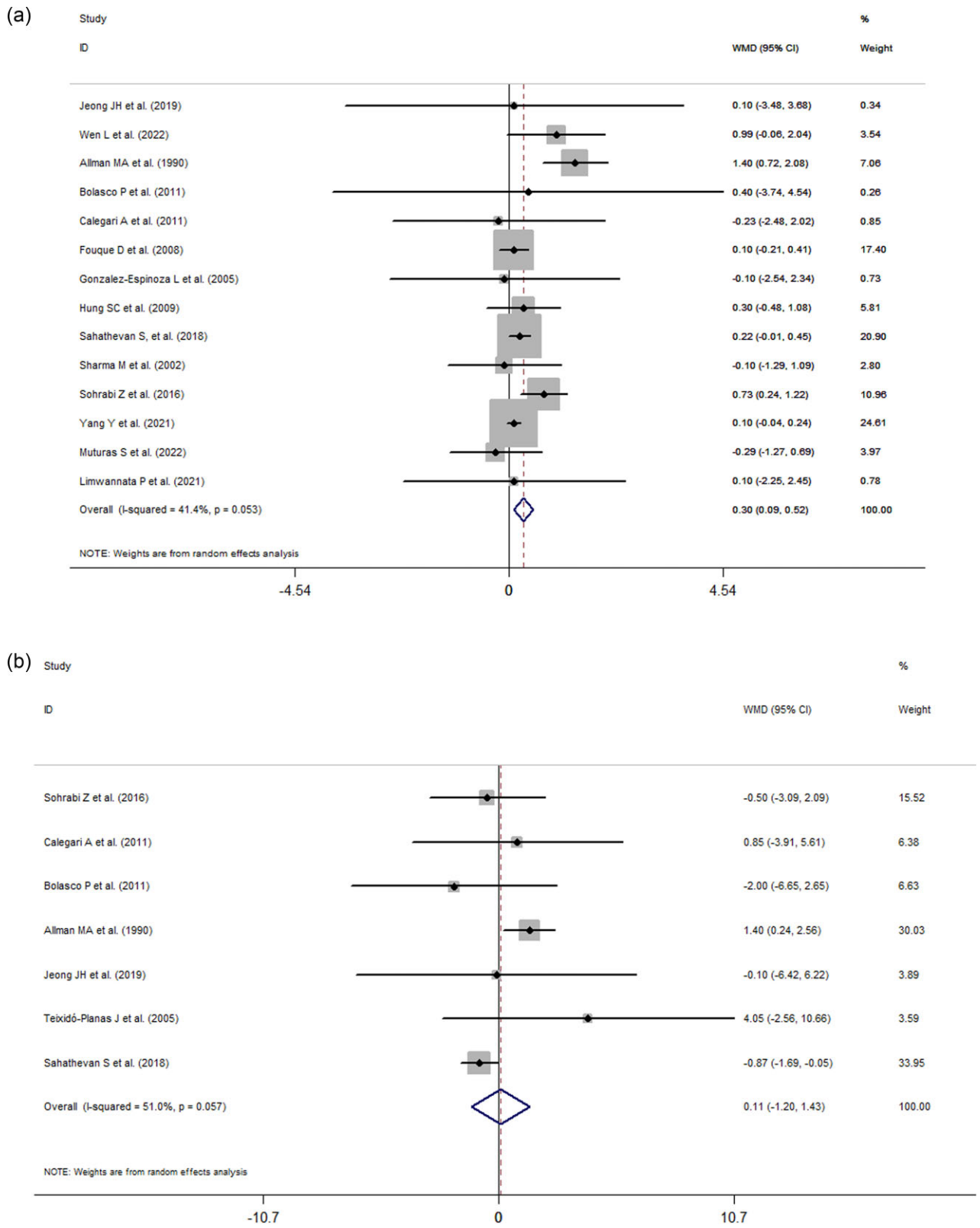

Figure 4: (a) Forest plots depicting the effect of ONS use on BMIs. (b) Forest plots depicting the effect of ONS use on lean body mass.

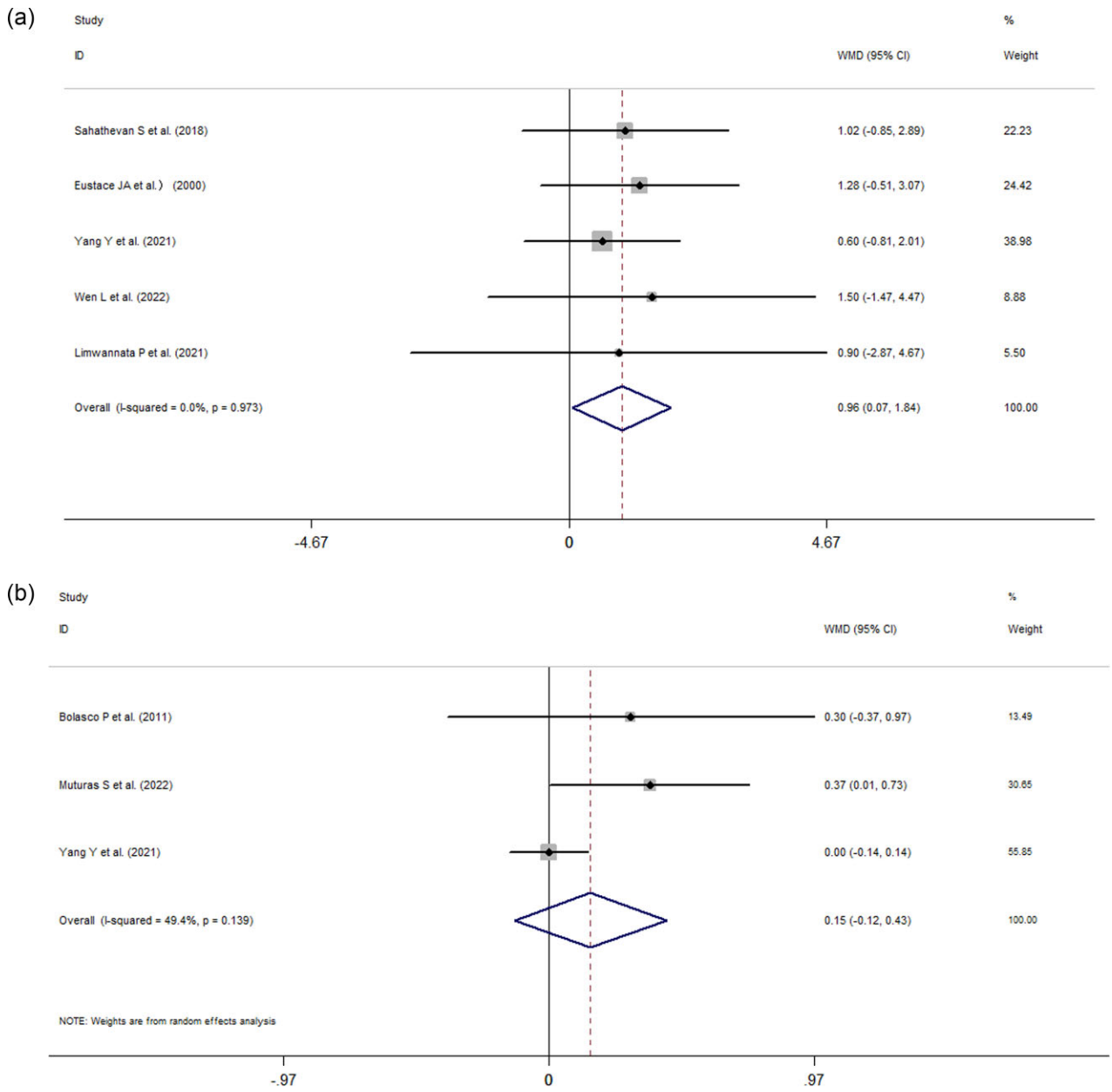

Figure 5: (a) Forest plots depicting the effect of ONS use on handgrip strength. (b) Forest plots depicting the effect of ONS use on the phase angle.

indicated that ONS use changed HGS by 0.96 kg (95% CI: 0.07 to 1.84, $P = 0.034$, $I^2 = 0\%$, $P = 0.973$; Fig. 5A) and the phase angle by 0.15° (95% CI: −0.12 to 0.43, $I^2 = 49.4\%$, $P = 0.274$; Fig. 5B).

Effects of ONS on electrolyte levels

Ten studies reported the effects of ONS use on serum phosphorus, and seven studies showed changes in potassium levels, respectively. Analyses of the pooled data revealed that ONS use did not significantly influence the serum phosphorus levels (−0.20 mg/dl, 95% CI: −0.58 to 0.18, $P = 0.306$, $I^2 = 69.9\%$; Fig. 6A) or serum potassium levels (0.03 mmol/l, 95% CI: −0.08 to 0.15, $I^2 = 0\%$, $P = 0.56$; Fig. 6B) of patients on dialysis.

Effects of ONS use on CRP levels

Data on the effects of ONS use on CRP levels were available only in three studies, and quantitative analysis indicated that ONS use did not significantly influence the CRP levels (−0.16 mg/l, 95% CI: −0.40 to 0.08, $I^2 = 49.4\%$, $P = 0.191$) of patients on dialysis (Fig. 7).

Sensitivity analysis

Considerable heterogeneity was observed in the effects of ONS use on albumin levels, which was one of the main observation parameters, despite subgroup analyses being conducted on potential variables. Although we sequentially omitted individual

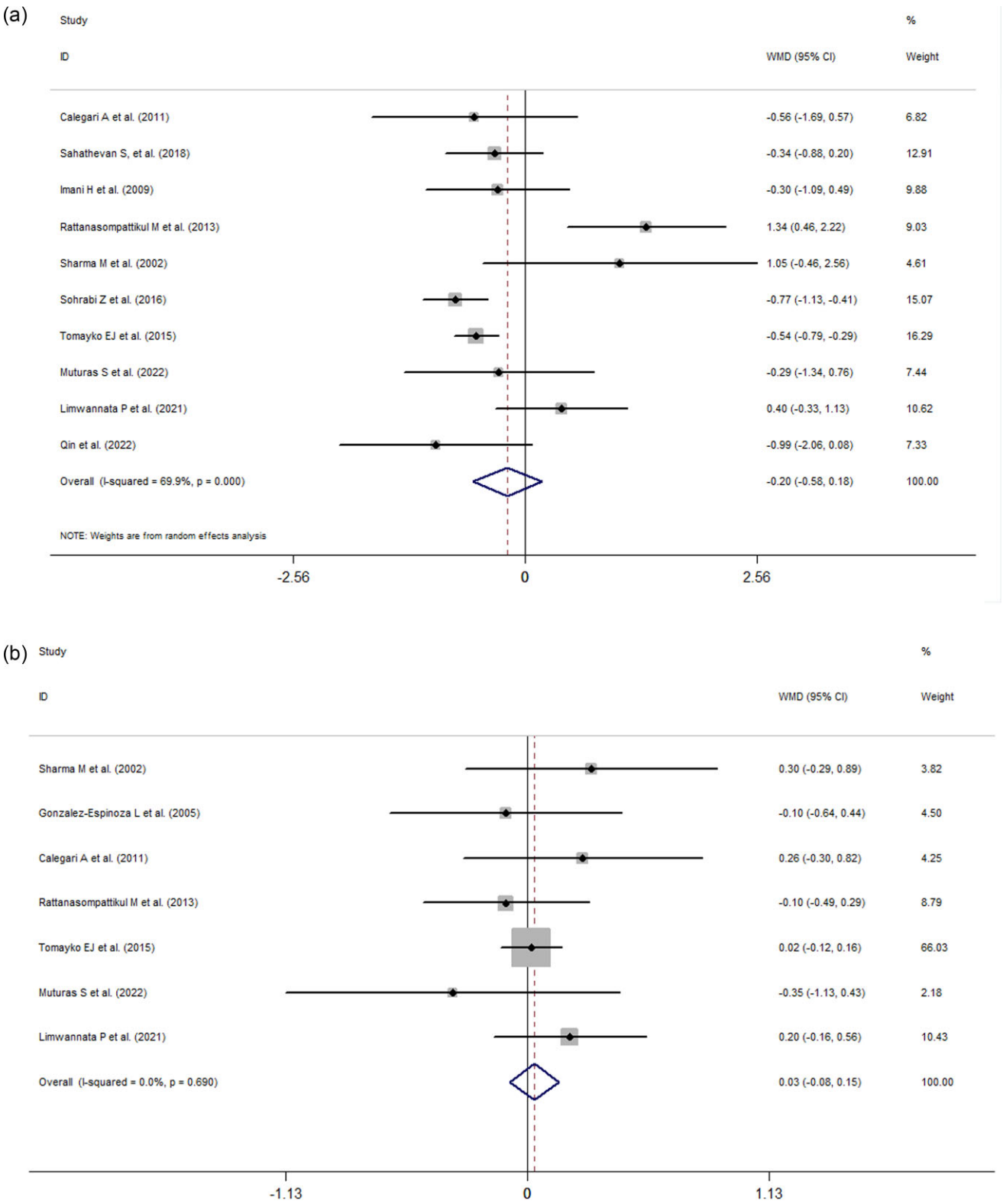

Figure 6: (a) Forest plots depicting the effect of ONS use on serum phosphorus levels. (b) Forest plots depicting the effect of ONS use on serum potassium levels.

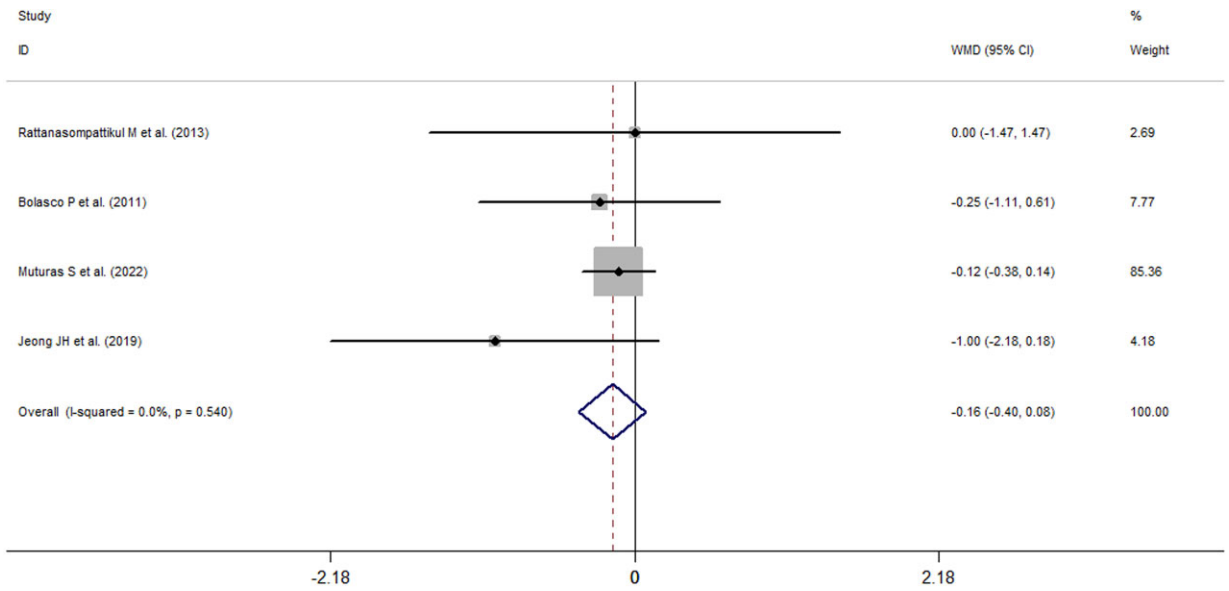

Figure 7: Forest plots depicting the effect of ONS use on C-reactive protein levels.

trials during sensitivity analysis, no single trial was determined to influence the albumin level outcomes (data not shown). The included studies were divided into high-quality (4–7 points) and low-quality (1–3 points) studies on the basis of their modified Jadad scale scores [48]. Low-quality studies [24–32, 34–36, 38, 40, 41, 43, 45] were excluded, and only five high-quality trials remained [23, 33, 37, 42, 44]. However, one of these studies was excluded because the unit albumin was presented in was "mg/dl," which was likely erroneous [23]. These steps reduced the heterogeneity to 21.8%, and pooled analysis indicated that ONS use increased serum albumin levels by 1.01 g/l (95% CI: 0.17–1.85, $P = 0.019$).

Publication bias

Potential publication bias was detected using funnel plots and the Egger test. The funnel plots of the effects of ONS use on serum albumin levels (Fig. 8A), BMI (Fig. 8B), and phosphorus levels (Fig. 8C) present an approximately symmetric pattern. The Egger test results also indicated no publication bias for the effects of ONS use on serum albumin levels ($t = 0.84$, $P = 0.361$), BMI ($t = 1.04$, $P = 0.319$), and phosphorus levels ($t = 1.77$, $P = 0.114$). Funnel plots were not created for the other variables (lean body mass, the phase angle, handgrip, potassium levels, and CRP levels) because the number of relevant studies that included the variables was <10.

DISCUSSION

We previously conducted a similar meta-analysis in which we quantitatively analyzed the effect of ONS use on serum albumin levels, BMI, and electrolyte levels. However, the quality of the analyzed evidence was very low [22]. Our current, updated systematic review and meta-analysis includes six additional RCTs assessing the effects of ONS use on the nutritional status, electrolyte levels, and inflammation of patients on dialysis. The main findings support that ONS administration can improve the nutritional status of patients on dialysis in terms of their albumin levels, BMIs, and handgrip strength without significantly altering their serum phosphorus and potassium levels. However, ONS use did not significantly affect lean body mass, the phase angle, and CRP levels.

PEW represents the progressive loss of bodily reserves of protein and energy fuels (body muscle and fat mass) and is common in patients on dialysis. A recent meta-analysis reported that the prevalence of PEW in patients on MDT was 28%–54% [4] and that its risk factors include inadequate dietary intake and additional nutrient loss (such as loss of amino acids, peptides, vitamins, trace elements, and glucose) during dialysis [7, 8, 49, 50]. However, the definition of PEW when applied for patients on dialysis is neither clear nor universally agreed on [51].

A low serum albumin level is a commonly used marker and an essential component of the diagnostic criteria of PEW [5] and can predict mortality in patients with MDT (HD or PD) [6, 52]. De Mutsert *et al.* [53] observed that a 1-g/dl decrease in the serum albumin level was associated with a 47% increased risk of mortality in patients on HD and 38% increased risk of mortality in patients on PD. According to Araujo *et al.* [54], a serum albumin concentration <3.5 g/dl was associated with higher odds of mortality in patients who had been on HD for >10 years. In addition, the sensitivity of measuring the serum albumin concentration to predict the outcomes of patients with CKD is high, and its granularity is as little as ≤2 g/l [55, 56]. By contrast, a prospective cohort study including patients on PD and HD reported that serum albumin levels cannot predict mortality risk and were not correlated with lean tissue index [57]. These discrepancies may be due to the differences in study population and durations of the studies. However, the latest KDOQI guidelines state that serum albumin may be used as a predictor of hospitalization and mortality for adults with CKD 5D on HD, with lower levels associated with a higher risk [6].

ONS use is common in malnourished patients in clinical settings or receiving family care, and it can be easily implemented to compensate an inadequate energy and protein intake from the diet. For adults with CKD of 3–5 stage at risk of or with PEW, the latest KDOQI guidelines suggest a minimum 3-month trial

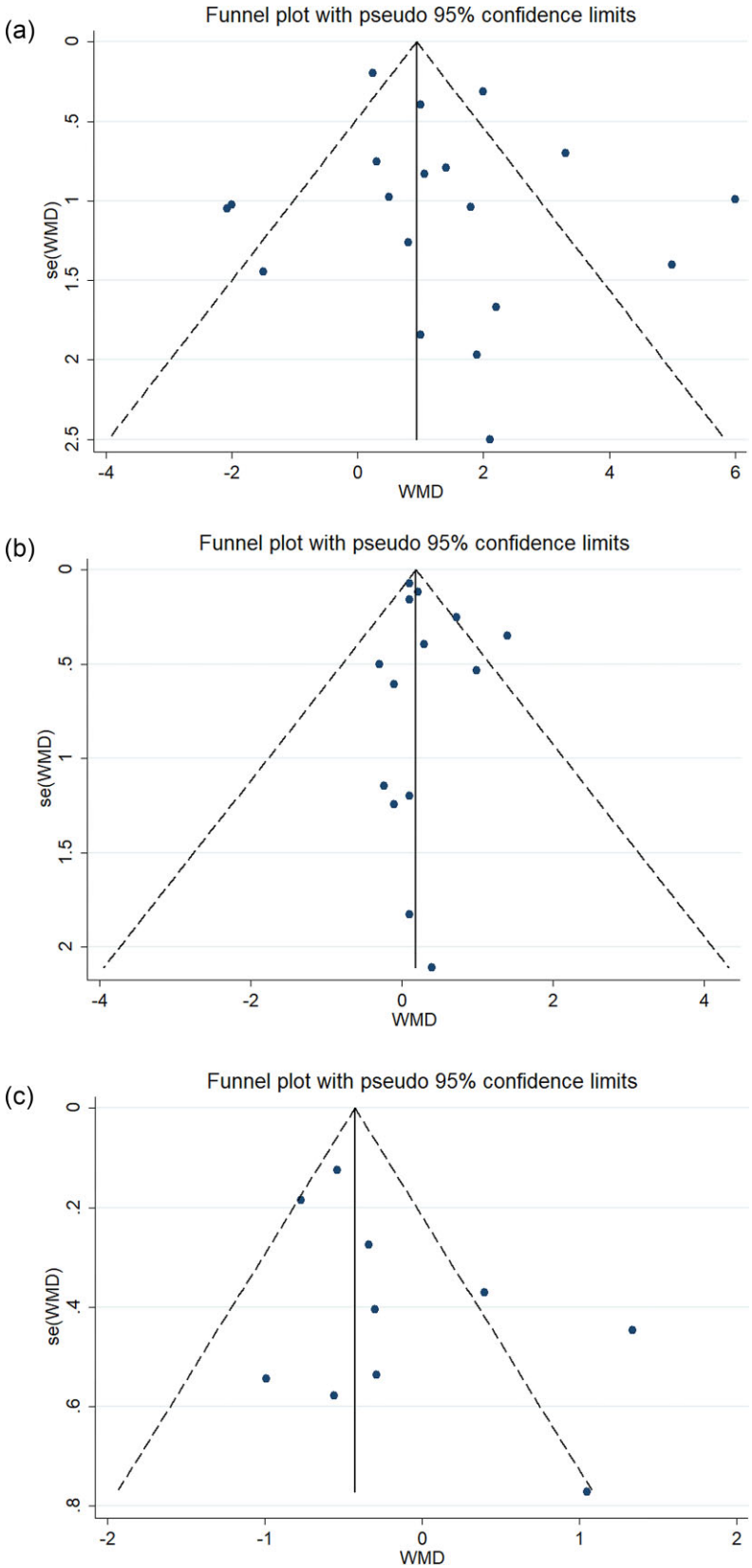

Figure 8: (a) Funnel plot for serum albumin levels. (b) Funnel plot for BMIs. (c) Funnel plot for serum phosphorus levels.

of ONS administration to improve nutritional status if dietary energy and protein intake does not meet nutritional requirements [6]. The results of our present meta-analysis and those of two previous reviews [39, 58] verify that ONS administration increases serum albumin levels. However, insufficient comparable data preclude the performance of a meta-analysis of its effects on mortality. Given the importance of albumin levels in predicting mortality risk, our results to some extent indicate that ONS use may improve the outcomes of patients on dialysis because it leads to increased albumin levels. However, notable heterogeneity was identified in both our current and previous meta-analyses regarding the overall effects of ONS use on serum albumin levels. Many factors, such as the type of dialysis, type or source of ONSs, patient's nutritional status, duration of intervention, patient compliance, supplementation timing, patient age, quality of the study, or patient comorbidities, may be involved in the generation of heterogeneity. Similar to the previous review [39], we conducted subgroup analyses of various potential factors, including the type of dialysis, duration of intervention, supplementation timing, types of ONSs, and nutritional status. However, heterogeneity remained in most of our subgroup analyses. In addition, we observed that non-intradialytic supplementation but not intradialytic supplementation significantly improved albumin levels. By contrast, many studies have reported that intradialytic nutrition can improve the nutritional status, inflammation, and biochemical measures (including albumin levels) of patients on HD [59]. Therefore, whether intradialytic nutrition is superior to providing similar support outside of dialysis treatment is worth exploring [59]. When stratified by study quality, the heterogeneity of the studies decreased, and the pooled effect on albumin remained significant, indicating that the heterogeneity was mainly the result of the differences in study quality.

For patients on dialysis, dietary restrictions are commonly imposed to limit potassium and phosphorus intake and prevent fluid overload [51]. Therefore, whether ONS use increases electrolyte disorders should be investigated. Among the studies assessing the effect of ONS use on phosphorus [23, 24, 27, 31, 33, 35, 38, 41, 44, 45], only two demonstrated significant changes in the phosphorus levels between the ONS and control groups after intervention [31, 46]; the pooled data indicated that ONS use had no significant influence on the serum phosphorus levels. We also discovered negative results related to potassium levels in the literature [23, 24, 29, 33, 38, 41, 44]. Our findings regarding phosphorus and potassium levels were in agreement with those of two systematic reviews [39, 58], indicating that ONS use has a very low probability of causing electrolyte disorders related to phosphorus and potassium in patients on MDT. However, the pooled results for phosphorus levels had high heterogeneity. Thus, the implementation of ONS treatment in clinical practice should be based on patients' specific conditions.

The nutritional status of patients with CKD should be monitored regularly. In adults with CKD 1–5D, dual-energy X-ray absorption remains the gold standard for measuring body composition [6]. Simple anthropometric parameters are also often used to reflect the nutritional status of patients on dialysis. Many studies have investigated the association of BMI with mortality in patients on HD and PD. BMI seems to play a different role in predicting the mortality risks for patients on HD and PD. Most studies have consistently reported a higher risk of mortality for patients on HD who were underweight and a lower risk for patients on HD who were overweight or obese [6, 60–62], whereas conflicting results have been reported for the morality in patients on PD [6, 63, 64]. The KDOQI 2020 guidelines indicate that underweight status (based on BMI) can be used as a predictor of higher mortality in patients on PD, whereas in patients on HD, a high BMI is paradoxically associated with a more favorable outcome [6]. In the present study, our result regarding BMI was inconsistent with that of the review by Mah *et al.* [39], who reported that oral protein-based supplements (versus placebo or no treatment) did not significantly improve the BMI of patients on dialysis. The difference in these results related to BMI may have arisen because of the following reasons. (i) The types of ONSs in the two reviews were different. In their review, Mah *et al.* [39] included only studies using protein-based ONSs, whereas we included studies using both protein-based and non-protein ONSs. (ii) Mah *et al.* included only papers published before 2020 [39], whereas we included five studies published in the last 2 years [41–45]. In addition, the effects of ONS use on lean body mass were analyzed in our study and that of Mah *et al.*, and we observed similar negative results to those reported in Mah *et al.* [39]. The results regarding BMI and lean body mass of our study indicate that ONS use improves fat mass in patients on dialysis.

Unlike other reviews [22, 39, 58], we analyzed the effects of ONS use on HGS and the phase angle. Patients on MDT often have low physical performance, which is associated with a high mortality rate, and HGS may be used as an indicator of protein-energy status, functional status, and all-cause mortality in patients on HD and PD [6, 65–67]. Notably, our study discovered that the HGS of patients on dialysis can be significantly improved using ONSs, indicating that ONS use may improve the muscle function of patients on dialysis. In addition, Mah *et al.* [39] found that protein-based ONSs may result in a higher serum prealbumin and mid-arm muscle circumference, especially in malnourished patients, suggesting that ONS use may be more beneficial for malnourished dialysis patients in terms of muscle mass. In our meta-analysis, only three studies reported the effects of ONS use on the phase angle [25, 42, 44], and the results they have reported are conflicting. A quantitative analysis of these studies did not reveal that ONS use improves the phase angle. In addition, neither the current review nor the review of Mah *et al.* has reported that ONS use can improve the CRP level. Moreover, the review of Mah *et al.* analyzed the effect of ONS use on interleukin-6 and obtained a negative result [39].

No consensus has been arrived at with respect to the type, time of initiation, or duration of use of enteral nutrition or nutritional supplementation for patients on MDT. Furthermore, few meta-analyses of this topic have been conducted. The strengths of our study are as follows: (i) compared with our previous review, this updated meta-analysis offers a more robust analysis of the effects of ONS use on the parameters reflecting the nutritional status of patients on dialysis, including HGS, lean body mass, and the phase angle, and it analyzed the marker of inflammation, which we failed to analyze in our previous study. (ii) Extensive subgroup analyses on the effects of ONS on serum albumin levels were conducted in this review, and the potential source of heterogeneity in the studies in this field was identified. Publication bias was analyzed not only by using funnel plots but also by using the Egger test. (iii) We summarized the suitable subgroups, durations, timings, and types of ONS interventions implemented for patients on dialysis, which could guide future research on this topic.

This study has several limitations. First, obvious heterogeneity was observed in the meta-analysis of the overall effects of ONS use on serum albumin levels. To investigate and minimize the source of heterogeneity, we performed many subgroup analyses. However, the heterogeneity remained after the subgroup

analyses based on the type of dialysis, duration of intervention, supplementation timing, types of ONSs, and nutritional status were performed. Furthermore, we grouped the included studies by quality and observed that the heterogeneity mainly arose from the studies' uneven quality. Therefore, our results should be interpreted cautiously, and ONS treatment should be suggested for patients on dialysis on the basis of the specific conditions of the individuals. Second, ~70% of the included studies had small sample sizes ($n < 60$), and >70% were of low quality, according to the modified Jadad scale [48]. These factors decrease the overall quality of the meta-analysis. Finally, we could not determine the effects of ONS use on the mortality risk or quality of life of patients on dialysis due to the current limited studies. Although our study investigated the effects of ONSs on inflammatory markers, only CRP was reported, and no other markers such as interleukin-6 were reported.

CONCLUSION

Our meta-analysis revealed that ONS use did not significantly affect phosphorus and potassium levels, lean body mass, the phase angle, and CRP levels but did significantly increase serum albumin levels, BMI, and HGS in patients on MDT. Thus, ONS use may improve the nutritional status and muscle function of patients on dialysis without aggravating electrolyte disturbances, such as those related to phosphorus and potassium. Large-scale, well-designed studies are warranted to verify these findings.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

Conceptualization was done by Y.K. and L.P.J.; methodology was developed by W.F., G.J., and Z.Y.; formal analysis was carried out by G.J., and L.P.J.; data were curated by G.J. and Z.Y.; the original draft preparation and writing were done by L.P.J., G.J., and Y.K.; review and editing of drafts was done by Y.K., L.P.J., and W.F.; supervision was carried out by Y.K. and Z.Y.; and funding was acquired by Y.K. and L.P.J. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

None declared.

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