*Review*

# Systematic Review of Nutrition Supplements in Chronic Kidney Diseases: A GRADE Approach

**Pei-Chin Lin** [1,2] , **Chu-Lin Chou** [3,4,5] , **Shih-Hsiang Ou** [6] , **Te-Chao Fang** [3,5,7,]* and **Jin-Shuen Chen** [1,6,8,]*

1  Department of Medical Education and Research, Kaohsiung Veterans General Hospital,
   Kaohsiung 813414, Taiwan; pclin@vghks.gov.tw
2  Department of Pharmacy, School of Pharmacy, Kaohsiung Medical University, Kaohsiung 807017, Taiwan
3  Division of Nephrology, Department of Internal Medicine, School of Medicine, College of Medicine,
   Taipei Medical University, Taipei 110301, Taiwan; chulin.chou@gmail.com
4  Division of Nephrology, Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University,
   New Taipei 235041, Taiwan
5  TMU Research Center of Urology and Kidney, Taipei Medical University, Taipei 110301, Taiwan
6  Division of Nephrology, Department of Internal Medicine, Kaohsiung Veterans General Hospital,
   Kaohsiung 813414, Taiwan; shou@vghks.gov.tw
7  Division of Nephrology, Department of Internal Medicine, Taipei Medical University Hospital, Taipei Medical
   University, Taipei 110301, Taiwan
8  School of Medicine, National Defense Medicine, Taipei 114201, Taiwan
*  Correspondence: fangtechao@gmail.com (T.-C.F.); dgschen@vghks.gov.tw (J.-S.C.);
   Tel.: +886-7-3468057 (T.-C.F.); +886-2-2737-181 (ext. 3577) (J.-S.C.)

**Abstract:** Chronic kidney disease (CKD) is cumulative worldwide and an increasing public health issue. Aside from the widely known protein restriction and medical therapy, less evident is the renal protection of nutrition supplements in CKD patients. This systematic review (SR), using a Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, aims to summarize and quantify evidence about the prevention effects of vitamin D and analogues, omega-3 polyunsaturated fatty acid (omega-3 PUFA), dietary fiber, coenzyme Q10 (CoQ10), and biotics on CKD progression. This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to examine SRs and/or meta-analysis of clinical controlled trials identified from PubMed, Embase, and the Cochrane Li;brary. Finally, seventeen SRs were included in the qualitative analysis. The beneficial effects of these nutrition supplements in CKD patients mostly seem to be at low to very low evidence on proteinuria, kidney function, and inflammations and did not appear to improve CKD prognosis. The recommendation of nutrition supplements in CKD patients needs to discuss with physicians and consider the benefits over the adverse effects. Longer follow-up of larger randomized trials is necessary to clarify the benefits of nutrition supplements in CKD patients.

**Keywords:** chronic kidney disease; vitamin D and analogues; omega-3 polyunsaturated fatty acid; dietary fiber; coenzyme Q10; biotics

## 1. Introduction

Chronic kidney disease (CKD), a gradual loss of kidney function, is an increasing public health issue. Over the past decades, CKD incidence is cumulative worldwide [1–3], paralleling epidemics in diabetes [4], hypertension [5], and metabolic syndrome [6]. Prevalence is estimated to be 8–16% worldwide [7]. Complications of CKD are associated with the risk of all-cause mortality, cardiovascular events, hospitalization, cognitive decline, and fracture [8–11]. Recently, some prognostic biomarkers are developed and helped to improve risk stratification and anticipate diagnosis of cardiovascular diseases [12]. However, CKD prognosis that is ameliorated by patient awareness and management strategies could be considered as an essential issue.

Dietary management to stop CKD progress has some benefits in patients with heavy proteinuria from some large trials [13,14], which were consistent with some reports from smaller-population trials [15–17]. The benefits of dietary protein restriction need to subsequently evaluate the problems of malnutrition and protein wasting syndrome [13,14]. Awareness of the disorder and strategies to reduce medical costs related to CKD need to be included in public policy and receiving increasing attention.

Aside from the widely known protein restriction and medical therapy, nutrition supplements have been reported to have a role in CKD prevention [18–25]. For example, a meta-analysis providing data for 688 patients has displayed that active vitamin D analogs reduced proteinuria (−16% (95% confidence interval (CI), −13% to −18%)) compared with controls (+6% (95% CI, 0% to +12%); $p < 0.001$) [18]. Additionally, the meta-analysis in diabetes patients indicated that vitamin D analogs provide beneficial effects on proteinuria and inflammation indexes [high-sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6) or tumor necrosis factor-alpha (TNF-$\alpha$)], but not on serum creatinine and estimated glomerular filtration rate (eGFR) [21]. However, other studies on meta-analysis have the contrary results of proteinuria protection [26,27]. Thus, the effects of vitamin D analogs on kidney disease merit to investigate and clarify in CKD patients.

In addition to vitamin D analogs, lower dietary acid loads (e.g., more fruits and vegetables and fewer meats and cheeses) had been reported to prevent CKD progress in clinical studies [19,20,24]. Other nutrition supplements [e.g., Omega-3 polyunsaturated fatty (Omega-3 PUFA), and biotics] had been reported to help maybe improve kidney function [22,23,25]. These nutritional supplements may have been used in a clinical application until now.

The SRs and/or meta-analysis are the level I study designs to answer the intervention question in clinical practice. Nevertheless, the previous SRs on the relationship between nutrition supplements and CKD were inconsistent and the evidence certainty was lacking. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach offers a transparent and structured process for developing and presenting summaries of evidence, including its effect size and certainty, and recommendations in health care. The objective of this systematic review was to determine the effects of current and relevant SRs of nutrition supplements on renal protection in CKD patients through using the GRADE approach.

## 2. Materials and Methods

### 2.1. Study Methods

This systematic reviews (SRs) was conducted and reported following the Preferred Reporting Items for SRs and Meta-Analyses (PRISMA) statement [28] to examine the renal protection effect of nutrition supplements in CKD (Table S1).

### 2.2. Search Strategy

We searched PubMed, Embase, and Cochrane CENTRAL databases for relevant SRs from the inception through October 2020. The strategy and keywords used for the systematic search were ("herbal supplements" OR "herbal supplement" OR "dietary supplements" OR "dietary supplement" OR "nutritional supplements" OR "nutritional supplement" OR supplementation* OR "nutrition supplements" OR "nutrition supplement" OR "health foods" OR "health food") AND (renal or kidney). We applied a high-sensitivity and high-specificity customized filter [29], a sensitivity of 96.0% and a specificity of 99.96%, for efficiently retrieving SRs. We also performed hand searches from the relevant studies of the included SRs to identify additional studies.

### 2.3. Selection Criteria

Inclusion criteria included: (i) study design: SRs and/or meta-analysis of clinically controlled trials (whether randomization was applied will be judged in quality assessment) designed to evaluate the influence of nutrition supplementation on renal protection in CKD

patients compared to placebo, regardless of language or publish date, (ii) population: any stages of CKD patients should not need dialysis or renal transplantation at baseline, (iii) intervention: nutrition or health supplements, (iv) comparison: placebo or other treatment, (v) renal protection outcomes: a study reported at least one clinical important issue or surrogate outcome data or outcome data can be extracted from subgroup analysis was available. The critical clinical outcomes included kidney function change from baseline and the risk of progression to end-stage renal disease (ESRD); the surrogate outcomes included inflammatory factors, for instances, hs-CRP, CRP, indoxyl sulphate (IS), or p-cresyl sulphate (PCS), and oxidative stress marker, malondialdehyde (MDA). Exclusion criteria: (i) nutrition supplement that has obtained FDA approval of drug license for CKD patients, (ii) Chinese herbal medicine, (iii) studies were presented as conference abstracts, case reports, letters to editors, or in vitro studies.

### 2.4. Data Extraction

A piloted form of data collection was created in excel, and two authors (Lin, Chou) extracted data from the included SRs independently. Collected variables included the first author, publish year, search databases, search duration, included study design and numbers, critical appraisal tool, population, intervention (dose and frequency if available), control group, outcomes related to kidney function, and nutrition supplement duration. Data were collected from publishing papers or online supplements, from study groups or subgroups. If the author provided the original data of included controlled trials and only used the text to describe the significance of effect size rather than presented the statistical data, we further calculated the effect size by author-reported statistical methods. Similarly, if the author only describes overall appraisal results rather than the present individual outcomes-related risk of bias, we further appraise the quality of the subgroup based on the data provided in the SR. Any discrepancies on data extraction or quality assessment were discussed and reached an agreement by consulting with the third author (Chen).

### 2.5. Grading of Recommendations Assessment, Development and Evaluation (GRADE) Grading the Evidence

We rate the certainty of included SRs using the GRADE approach as adopted for the "summary of findings" table. GRADE specified the quality of evidence to four categories—high, moderate, low, and very low. If the context of an SR comes from randomized-controlled trials, the evidence category begins as high-quality. There are five reasons to possibly rate down 1–2 grade of evidence, including the risk of bias (most information comes from studies at moderate or high risk of bias), imprecision (the sample size or "optimal information size" [OIS] criterion is not met or the 95% CI overlap no effect), inconsistency (substantial heterogeneity between studies and unexplained, $I^2$ more than 50% was set as substantial heterogeneity) [30], indirectness (depend on the extent of differences between our interests and the SR on patient populations, interventions, measurements of the outcome, and the methods of the trials of the candidate interventions) and publication bias (asymmetric funnel plots presented, Deeks' test or the trim and fill method of non-significance, or included studies come from several small studies and most of which were commercially funded) [31–37].

### 2.6. Data Synthesis and Statistics

Since the included SRs, aim to evaluate the renal protection effect on the same nutrition supplement, may consist of duplicated RCTs and thus become independent, we abandoned to summarize the data by a statistical method and present the result as an SR. If standardized mean difference (SMD) was used in an SR to show the pooled outcome measure; we considered a SMD of 0.2, 0.5, and 0.8 a small, moderate, and large effect, respectively [38]. We used GRADEpro GDP software (GRADEpro GDT: GRADEpro Guideline Development Tool (Software). McMaster University, 2020 (developed by Evidence Prime, Inc.: Hamilton, ON, Canada). Available from gradepro.org.) to synthesis and present the certainty and summary of findings for the included SRs.

## 3. Results

### 3.1. Baseline Information of Included SRs

We identified 666 articles from the electronic databases searching, excluding duplicates, irrelevant, and not fulfilled the inclusion criteria and left 13 SRs. Furthermore, we retrieved 4 SRs by hand searching from the reference lists of relevant studies, eventually included 17 SRs in this SR. Figure 1 outlined the process of systematic search and adding a PRISMA flow diagram. PRISMA checklist was provided as supplementary material (Table S1).
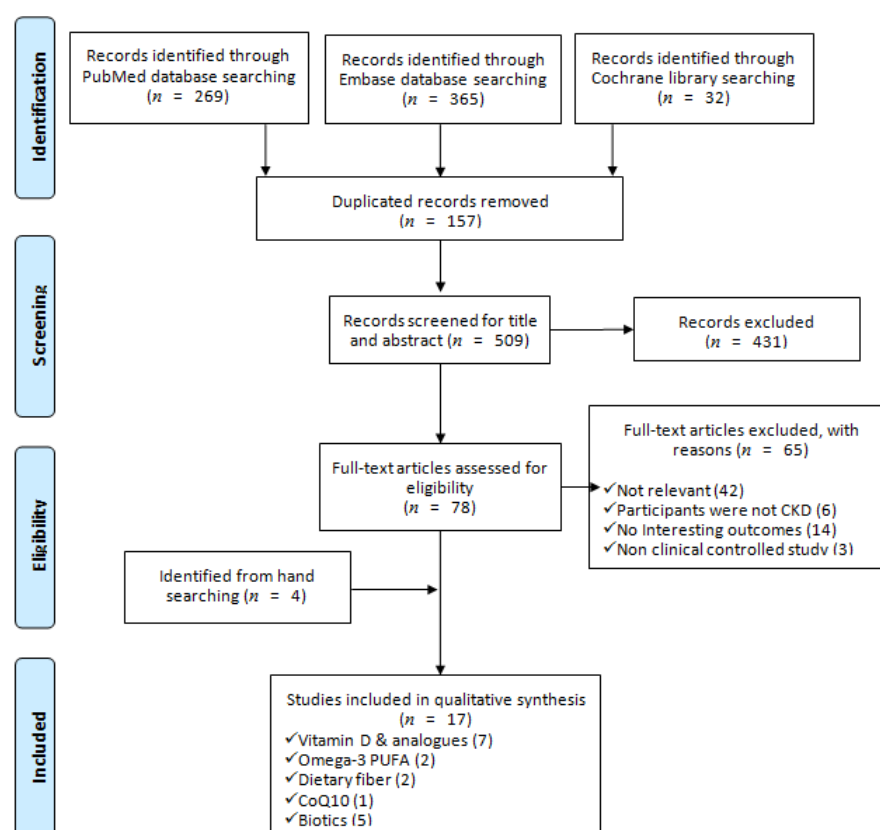


**Figure 1.** PRISMA flow diagram of including systematic reviews in this study [28].

Among the included SRs, 7, 2, 2, 1 and 5 studies aim to evaluate the renal protective effects of vitamin D and analogs [21,26,27,39–42], Omega-3 PUFA [22,43], dietary fiber [24,44], coenzyme Q10 (CoQ10) [45], and biotics [23,25,46–48], respectively. All of the included SRs performed the search on at least three databases, and the majority of searching, except for Zhang et al. study [48], had no restriction on publication date. Five SRs evaluated the effects of nutrition supplements in diabetic nephropathy patients only, and the others in any stages and any etiologies of CKDs. The most used appraisal tools for included RCRs was a Cochrane risk of bias (RoB), 10 SRs were using this checklist. Additionally, there were 2, 1 and 1 studies using the Jadad Scale, Newcastle-Ottawa Scale, and Heyland Methodological Quality Score to appraise the quality of included RCTs, respectively. Moreover, one study assessed the quality by RoB and GRADE simultaneously. In the SRs of vitamin D and analogues, 4 assessed the effects of established vitamin D compounds (vitamin D2, eregocalcifefol, ercalcidiol, ercalcitriol, vitamin D3, cholecalciferol, carcidiol, calcitriol) or the newer analogues (paricalcitol and doxercalcigerol) [26,40–42], the others only focused on established compounds. In the biotics SRs, 2 focused on the effect of probiotics [46,47], 1 on probiotics or prebiotics [25], and 2 on probiotics, prebiotics or synbiotics [23,48]. The included clinically controlled trials in all SRs received nutrition supplements at least 1 week. All detailed information of the included SRs was presented in Table 1.

**Table 1.** Baseline information of included systematic reviews.

| Author Year | Search Databases | Search Duration (Through) | Included Study Design | Study No. | Critical Appraise Tool | Population | Intervention | Control | Outcomes Related to Kidney Function | Treatment Duration |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | **Vitamin D and Analogues** | | | | | |
| Gupta 2019 [26] | PubMed, Scopus, and Google scholar | January 2018 | RCTs | 9 T2DN (7) T1DN (1) NA (1) | RoB | DN | calcitriol 0.25–0.5 mcg QD-BIW or 50,000IU QW paricalcitol 1–2 mcg QD cholecalciferol 50,000IU QW vitamin D3 50,000IU QM | placebo | UACR, UPCR, 24-h urine protein excretion, UAER, SCr, | 8–24 weeks |
| Milajerdi 2019 [39] | EMBASE, Scopus, PubMed, Cochrane Library, and Web of Science | November 2018 | clinical trials | 17 non-dialysis (6)dialysis (11) | Cochrane RoB | CKD with or without dialysis | Calcitriol 0.03 mc/kg BIW−0.5 mcg/day Vitamin D3 4662–350000IU/week (QD QW Q2W QM) ergocalciferol 50,000 IU QW-QM | placebo | CRP | 3 and 52 weeks |
| Wang 2019 [21] | Pubmed, Embase, Cochrane Library, CNKI, WANGFANG and VIP | September 2007~July 2018 | RCTs | 20 T2DN (8) T1DN+T2DN (12) | Cochrane RoB | DN | calcitriol 0.14–1 mcg/day (QD, BIW) alfacalcidol 0.25–0.5 mcg/day cholecalciferol 800 IU/day Vitamin D3 50,000 IU/day | placebo or blank treatment | 24-h urine protein; UAER; SCr; eGFR; hs-CRP; TNF-α; IL-6 | 8–24 weeks |
| Zhang 2017 [42] | PubMed, Embase, Scopus, Index Copernicus, DOAJ, CNKI, and Wanfang | January 2017 | RCTs | 24 T2DN (17) T1DN (1) NA (6) | Newcastle–Ottawa scale | DN DN (20) DN+Vit.D deficient (4) | alfacalcidol calcitriol cholecalciferol paricalcitol | placebo | 24-h proteinuria, UACR, hs-CRP, SCr | 6–24 weeks |
| Derakhshanian 2015 [27] | PubMed, SCOPUS, and Google Scholar | September 2014 | RCTs (4), cross-sectional studies (6) | 10 | RCTs: Jadad score Cross-sectional studies: Newcastle—Ottawa Scale | DN | RCTs cholecalciferol 5600–50,000 IU/week (QD, QW) calcitriol 20 IU/day | placebo | UACR | RCTs 6–24 weeks |
| Zhao 2014 [41] | Pubmed, Embase, Sinomed, CNKI, Wanfang and clinical trial register centers | 1 January 2014 | RCTs | 20 | RoB | DN | Vitamin D3, paricalcitol, cholecalciferol, calcitrio, alfacalcidol | placebo or blank control | Change of 24-h proteinuria from baseline, UACR, urine microalbumin | F/U: 4–48 weeks |
| Xu 2013 [40] | PubMed, EMBASE and OvidSP | September 2012 | RCTs | 18 | Cochrane risk of bias | CKD without dialysis or renal transplantation | cholecalciferol 7000–75,000 IU/week (QD, QW, QM) calcitriol 0.25–0.5 mcg QD-BIW paricalcitol 0.86–4 mcg/day, QDTIW doxercalcigerol 1 mcg/day alfacalcidol 0.25–1 mcg QD | placebo or no medication | 24 hr-urine protein, UACR, eGFR, CCr | study duration: 1–24 months |

**Table 1.** *Cont.*

| Author Year | Search Databases | Search Duration (Through) | Included Study Design | Study No. | Critical Appraise Tool | Population | Intervention | Control | Outcomes Related to Kidney Function | Treatment Duration |
|---|---|---|---|---|---|---|---|---|---|---|
| **Omega-3 polyunsaturated fatty acid (n-3 PUFA)** | | | | | | | | | | |
| Saglimbene 2020 [22] | MEDLINE, Embase, and CENTRAL | 12 January 2018 | RCTs or quasi RCTs | 60 CKD stage 1–5 (20) dialysis (24) transplant (16) | GRADE | adults and children with CKD across all stages | Fish or n-3 PUFA supplementation (0.4–12 g/day) | placebo, standard care, or any other treatment | ESKD, acute transplant rejection, and allograft loss | treatment and F/U: 1–48 months |
| Hu 2017 [43] | PubMed, Embase, and Cochrane Library | October 2014 | RCTs | 9 CKD IgA nephropathy (7) ADPKD (1) | Jadad score | CKD (not on ESRD) | EPA 1.8–10 g/d, fish oil 6 g/day omega-3 capsules 4 g/day PUFAs 3.0 g/day | placebo, ACEI/ARB, low dose EPA and DHA, RASB, corn oil, olive oil | proteinuria, CCR, eGFR, occurrence of ESRD | F/U: 2–76.8 months |
| **Dietary fiber** | | | | | | | | | | |
| Wu 2019 [44] | PubMed, Web of Science and Cochrane Library | 1 September 2017 | clinical controlled trials; RCTs (6) pre-post trials (6) | 12 RCTs (6) pre-post trials (6) | Heyland Methodological Quality Score * | stage 3–5 of CKD with or without dialysis | dietary fibre intake 7.5–25 g/day | placebo | IS, PCS | mean 5 weks 2.1–10 weeks |
| Chiavaroli 2015 [24] | MEDLINE, EMBASE, CINHAL and Cochrane Library | 1 September 2014 | controlled feeding trials | 14 non-dialysis(10) HD (4) | Heyland Methodological Quality Score * | CKD with or without dialysis | dietary fiber intake (median fiber dose 26.9 g/day (range 3.1–50.0 g/day)) | non-fiber supplemented diets or low-fiber diets | serum urea, SCr | F/U median 4.5 weeks (range:1.4–20 weeks) |
| **Coenzyme Q10 (CoQ10)** | | | | | | | | | | |
| Zhang 2019 [45] | PubMed, Web of Science, Ovid-Medline, ProQuest, Science Direct, Springer link et al. ** | June 2018 | RCTs (4), experimental studies (4) | 8 | Cochrane risk of bias | type 1 or 2 diabetic kidney disease | CoQ10 (30–1000 mg/day) in combination with western medicine or CoQ10 | western medicine or placebo | eGFR, Serum Urea, BUN, Scr | 12 weeks |

**Table 1.** *Cont.*

| Author Year | Search Databases | Search Duration (Through) | Included Study Design | Study No. | Critical Appraise Tool | Population | Intervention | Control | Outcomes Related to Kidney Function | Treatment Duration |
|---|---|---|---|---|---|---|---|---|---|---|
| **Probiotics, Prebiotics, Synbiotics** | | | | | | | | | | |
| Zheng 2020 [48] | PubMed, Cochrane CENTRAL, and the Web of Science | 1 January 2000~15 May 2019 | RCTs | 13 CKD stages 2–4 (2) HD (7) DN (4) | Cochrane ROB | DN | Probiotics alone or associated with prebiotics (synbiotics) | placebo | CRP | 4–12 weeks |
| McFarlane 2019 [25] | MEDLINE, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials, and International Clinical Trials Register and clinicaltrials.gov | July 2017 | RCTs | 16 non-dialysis (8)HD (7) PD (1) | Cochrane RoB | adults and children CKD with or without dialysis | prebiotic 2.3–50 g/day probiotic $11 \times 10^6$–$2 \times 10^{12}$ CFU/day | placebo | eGFR, SCr, proteinuria, serum urea, free and protein-bound concentrations of serum IS and PCS, progression to ESKD | 1–24 weeks |
| Tao 2019 [47] | PubMed, Embaseand Cochrane | September 2018 | RCTs | 10 non-dialysis (4) HD (5) PD (1) | Cochrane RoB | CKD with or without dialysis | probiotic supplementation $2 \times 10^9$–$1.8 \times 10^{11}$ CFU/day | placebo | urea, uric acid, CRP, SCr, eGFR | 6–24 weeks |
| Jia 2018 [46] | PubMed, EMBASE and Cochrane Library | 31 March 2018 | RCTs | 8 non-dialysis (4) HD (3) PD (1) | Cochrane RoB, GRADE | CKD with or without dialysis | Probiotics: $4 \times 109$–$1.8 \times 1011$ CFU/day | placebo | BUN, SCr, CRP, IL-6 | 6–24 weeks |
| Pisano 2018 [23] | Ovid-MEDLINE, PubMed and CENTRAL | 5 March 2018 | RCTs | 17 non-dialysis (10) HD (5) PD (1) transplant (1) | Cochrane renal group, risk of bias | CKD or ESKD on chronic renal replacement | prebiotics 20–50 g/day, probiotics 2# tid; $2 \times 10^9$–$9 \times 10^{10}$ CFU/day synbiotics: 3–6#/day;1 5 gm powder/day; $1.1 \times 10^7$ CFU+inulin 2.31 g/day; 15 g powder+2#/day | placebo or standard therapy | CCr, eGFR, SCr, albuminuria, CRP, serum urea, TNF-α; IL-6 | 4–24 weeks |

*: scores equal to or more than 8 is considered of high methodological quality (high MQS). **: 12 databases were searched, PubMed, Web of Science, Ovid-Medline, ProQuest, Science Direct, Springer link, Wiley Library Online, Chinese BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese medical Citation Index (CMCI), Chinese Scientific Journal Database (VIP), and Wanfang database. RCTs: randomized controlled trials; RoB: risk of bias; DN: diabetic nephropathy;T2DN: type 2 diabetic nephtopathy; T1DN: type 1 diabetic nephtopathy; NA: not available; UACR: urine albumin creatinine ratio; UPCR: urine protein creatinine ratio; UAER: urinary albumin excretion rate; SCr: serum creatinine; CKD: chronic kidney disease; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; hs-CRP: high-sensitivity C-reactive protein; TNF-α: tumor necrosis factor-alpha; IL-6: interleukin 6; CCr: creatinine clearance; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ESKD: end-stage kidney disease; ESRD: end-stage renal diseases; IS: Indoxyl sulphate; PCS: p-cresyl sulphate; ESKD: end-stage kidney diseases; CFU: colony-forming unit; BUN: blood urea nitrogen; MDA: malondialdehyde.

### 3.2. Grading of Recommendations Assessment, Development and Evaluation (GRADE) Qualifying the Evidence

Only four clinical important outcomes (urinary albumin excretion rate (UAER), reduced proteinuria, the occurrence of ESRD, serum urea) and one surrogate outcome (CRP) reported in the five individual SRs [27,40,43,47,48] reached the moderate level of certainty, the other evidence rated low to very low (Tables 2 and 3). The most being downgraded domain was the risk of bias in included RCTs. In this SR, several outcome data were extracted from subgroup analysis in the original SR. Although the overall quality of the primary outcome may be presented as low or unclear risk of bias, the other outcome-specific risks of bias were not assessed and reported. Thus, downgrading one point was performed. Furthermore, nine clinical relevant outcome evidence presented a high risk of bias in more than half of RCTs; we downgraded two points to very severe in the domain of risk of bias. In the domain of indirectness, we downgraded all surrogate outcomes one point to severe; on the contrary, the clinically relevant outcomes were not treated the same.

### 3.3. Vitamin D and Analogues on Renal Protection

Five SRs focused on diabetic nephropathy reported 13 clinical relevant outcome data. In very low to low certainty evidence of vitamin D and analogues (established vitamin D compounds) appeared to reduce urinary albumin excretion rate (UAER) (2 SRs, included two and eight RCTs, respectively, mean difference −0.39, 95% CI −0.71 to −0.07 and −67.36, 95% CI −91.96 to −42.76). The vitamin D and analogue effect on urine albumin creatinine ratio (UACR) varied in the included SRs. Very low to moderate certainty evidence showed no significant impact on SRs only enrolled supplement with established vitamin D compounds. SRs included RCTs with receiving newer vitamin D analogue (paricalcitol or doxercalciferol) rather than established compounds alone suggested a significant decrease in UACR (two SRs, included eight and four RCTs, respectively, mean difference −0.49, 95% CI −0.9 to −0.08 and SMD −0.29, 95% CI −0.48 to −0.1). However, the effect seems small, and the evidence was very low. In very low to low certainty of evidence suggested vitamin D and analogues reduce proteinuria 0.23–0.26 gm per 24 h (2 SRs, included 11 and 14 RCTs, respectively, mean difference −0.26, 95% CI −0.34 to −0.17 and −0.23, 95% CI −0.3 to −0.15). The effect on serum creatinine varied and the certainty of the evidence was very low. Only one SR reported vitamin D and analogues does not affect urine protein creatinine ratio (UPCR) and eGFR, respectively (Tables 2 and 4).

Two SRs focused on diabetic nephropathy reported four surrogate outcome data. Very low certainty of evidence suggested Vitamin D and analogues decreased the inflammatory markers of hs-CRP, IL-6, and TNF-α (hs-CRP: MD −0.80 to −0.69; IL-6: −0.73; TNF-α: −56.79), as shown in Table 3.

One SR of vitamin D analogues, as compared with placebo, was investigated on renal protection in CKD patients. Moderate certainty evidence showed significantly reduced proteinuria (relative risk of reduced proteinuria 2.0, 95% CI 1.42 to 2.81) (Tables 2 and 4).

**Table 2.** Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach evidence certainty and summary of findings of the clinical important outcomes.

| Author year | Outcomes | No of Studies | Certainty Assessment | | | | | Certainty | Summary of Findings | |
| | | | Risk of Bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall Certainty of Evidence | Relative Effect (95% CI) | Risk Difference with Nutrition Compared to Placebo (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | **Vitamin D and Analogues** | | | | | |
| Gupta 2019 [26] | UAER | 2 RCTs | serious [a] | serious [b] | not serious | not serious | none | ⊕⊕◯◯ LOW | - | MD **0.39 lower** (0.71 lower to 0.07 lower) |
| | UACR | 5 RCTs | very serious [c] | not serious | not serious | serious [d] | none | ⊕◯◯◯ VERY LOW | - | MD **0.14 lower** (0.34 lower to 0.06 higher) |
| | UPCR | 1 RCT | serious [e] | not serious | not serious | serious [d] | none | ⊕⊕◯◯ LOW | - | MD **0.19 lower** (0.9 lower to 0.51 higher) |
| Wang 2019 [21] | eGFR | 4 RCTs | serious [f] | not serious | not serious | serious [d] | publication bias strongly suspected [g] | ⊕◯◯◯ VERY LOW | - | MD **2.13 higher** (2.06 lower to 6.32 higher) |
| | SCr | 9 RCTs | serious [f] | not serious | not serious | serious [d] | publication bias strongly suspected [g] | ⊕◯◯◯ VERY LOW | - | MD **0.83 lower** (3.67 lower to 2.02 higher) |
| | Proteinuria (g/24 h) | 11 RCTs | serious [f] | not serious [h] | not serious | not serious | publication bias strongly suspected [g] | ⊕⊕◯◯ LOW | - | MD **0.26 lower** (0.34 lower to 0.17 lower) |
| | UAER | 8 RCTs | serious [f] | very serious [i] | not serious | not serious | publication bias strongly suspected [g] | ⊕◯◯◯ VERY LOW | - | MD **67.36 lower** (91.96 lower to 42.76 lower) |
| Zhang 2017 [42] | Proteinuria (g/24 h) | 14 RCTs | serious [j] | very serious [i] | not serious | not serious | none | ⊕◯◯◯ VERY LOW | - | MD **0.23 lower** (0.3 lower to 0.15 lower) |
| | UACR | 8 RCTs | serious [j] | serious [b] | not serious | not serious | none | ⊕⊕◯◯ LOW | - | MD **0.49 lower** (0.9 lower to 0.08 lower) |
| | SCr | 9 RCTs | serious [j] | serious [b] | not serious | serious [d] | none | ⊕◯◯◯ VERY LOW | - | SMD **0.16 SD lower** (0.42 lower to 0.11 higher) |
| Derakhshanian 2015 [27] | UACR | 4 RCTs | not serious | not serious | not serious | serious [d] | none | ⊕⊕⊕◯ MODERATE | | MD **17.99 higher** (35.36 lower to 71.33 higher) |
| Zhao 2014 [41] | Proteinuria (g/24 h) | 9 RCTs | very serious [k] | not serious | not serious | not serious | publication bias strongly suspected [l] | ⊕◯◯◯ VERY LOW | - | MD **0.44 lower** (0.54 lower to 0.34 lower) |
| | UACR | 4 RCTs | very serious [k] | not serious | not serious | not serious | publication bias strongly suspected [l] | ⊕◯◯◯ VERY LOW | - | SMD **0.29 SD lower** (0.48 lower to 0.1 lower) |
| Xu 2013 [40] | eGFR | 12 RCTs | serious [f] | not serious | not serious | serious [d] | none | ⊕⊕◯◯ LOW | - | SMD **0.1 SD lower** (0.24 lower to 0.03 higher) |
| | risk of dialysis initiation | 4 RCTs | serious [f] | not serious | not serious | serious [d] | none [m] | ⊕⊕◯◯ LOW | **RR 1.48** (0.54 to 4.03) | |
| | reduced proteinuria | 6 RCTs | serious [f] | not serious | not serious | not serious | none [m] | ⊕⊕⊕◯ MODERATE | **RR 2.00** (1.42 to 2.81) | |

**Table 2.** *Cont.*

| Author year | Outcomes | No of Studies | Risk of Bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall Certainty of Evidence | Relative Effect (95% CI) | Risk Difference with Nutrition Compared to Placebo (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Certainty Assessment | | | | Certainty | Summary of Findings | |
| **Omega-3 Polyunsaturated Fatty Acid (Omega-3 PUFA)** | | | | | | | | | | |
| Saglimbene 2020 [22] | GFR | 6 RCTs | serious [a] | not serious | not serious | serious [d] | none | ⊕⊕○○ LOW | | SMD **0.22 SD** higher (0.03 lower to 0.48 higher) |
| | progression to ESKD | 3 RCTs | serious [a] | serious [n] | not serious | serious [n] | none [m] | ⊕○○○ VERY LOW [n] | **RR 0.3** (0.09 to 0.98) | |
| | SCr | 7 RCTs | serious | serious [o] | not serious | serious [d] | none [m] | ⊕○○○ VERY LOW | - | MD 2.20 higher (17.63 lower to 22.03 higher) |
| | Proteinuria (g/24 h) | 6 RCT | serious | not serious | not serious | serious [d] | none [m] | ⊕⊕○○ LOW | - | MD 0.16 lower (0.48 lower to 0.15 higher) |
| Hu 2017 [43] | CCr | 6 RCTs | serious [p] | serious [b] | not serious | serious [d] | none | ⊕○○○ VERY LOW | - | SMD **0.22 SD** higher (0.40 lower to 0.84 higher) |
| | eGFR | 6 RCTs | serious [p] | not serious | not serious | serious [d] | none | ⊕⊕○○ LOW | | SMD **0.14 SD** higher (0.13 lower to 0.42 higher) |
| | the occurrence of end-stage renal disease | 3 RCTs | serious [p] | not serious | not serious | not serious | none [m] | ⊕⊕⊕○ MODERATE | **RR 0.49** (0.24 to 0.99) | |
| | Proteinuria (g/24 h) | 7 RCTs | very serious [k] | not serious | not serious | not serious | none | ⊕⊕○○ LOW | - | SMD **0.31 SD** lower (0.53 lower to 0.10 lower) |
| **Dietary Fiber** | | | | | | | | | | |
| Chiavaroli 2015 [24] | SCr | 8 RCTs | very serious [k] | not serious | not serious | serious [d] | none [m] | ⊕○○○ VERY LOW | | MD **21.97** lower (52.22 lower to 8.28 higher) |
| | serum urea | 9 RCTs | very serious [k] | serious [b] | not serious | serious [d] | none [m] | ⊕○○○ VERY LOW | | MD **2.35** lower (4.78 lower to 0.08 higher) |
| **Coenzyme Q10 (CoQ10)** | | | | | | | | | | |
| Zhang 2019 [45] | serum urea | 2 RCTs | serious [q] | very serious [i] | not serious | serious [d] | none | ⊕○○○ VERY LOW | - | SMD 1.24 **SD** lower (4.04 lower to 1.55 higher) |

**Table 2.** *Cont.*

| | | | Certainty Assessment | | | | | Certainty | Summary of Findings | |
|---|---|---|---|---|---|---|---|---|---|---|
| Author year | Outcomes | No of Studies | Risk of Bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall Certainty of Evidence | Relative Effect (95% CI) | Risk Difference with Nutrition Compared to Placebo (95% CI) |
| | | | | Probiotics, Prebiotics, Synbiotics | | | | | | |
| McFarlane 2019 [25] | serum urea | 4 RCTs | very serious [k] | not serious | not serious | not serious | none | ⊕⊕○○ LOW | - | MD **2.12 lower** (3.86 lower to 0.37 lower) |
| Tao 2019 [47] | serum urea | 2 RCTs | not serious | serious [b] | not serious | not serious | none | ⊕⊕⊕○ MODERATE | - | MD **30.01 lower** (56.78 lower to 3.25 lower) |
| Jia 2018 [46] | BUN | 1 RCT | very serious [r] | not serious | not serious | serious [d] | none | ⊕○○○ VERY LOW | - | MD **5.78 lower** (21.42 lower to 9.86 higher) |
| | SCr | 3 RCTs | very serious [k] | not serious | not serious | serious [d] | none | ⊕○○○ VERY LOW | - | MD **0.10 higher** (0.11 lower to 0.31 higher) |
| Pisano 2018 [23] | SCr | 7 RCTs | very serious [k] | not serious | not serious | serious [d] | none | ⊕○○○ VERY LOW | - | MD **0.02 lower** (0.09 lower to 0.05 higher) |
| | serum urea | 5 RCTs | very serious [k] | not serious | not serious | serious [d] | none | ⊕○○○ VERY LOW | - | SMD **0.20 SD lower** (0.41 lower to 0.01 higher) |

The bold of the words in the columns of "summary of findings" means a statistical significance. CI: Confidence interval; MD: Mean difference; SMD: Standardized mean difference; RR: Risk ratio. Explanations: [a]. attrition bias observed in included studies; [b]. substantial heterogeneity ($I^2 > 50\%$) and cannot find the source of heterogeneity; [c]. bias in allocation concealment, blinding process, or outcome measure in majority of included studies; [d]. the pooled estimate cannot exclude no effect; [e]: bias occurred in randomization, allocation concealment and blinding process; [f]: the majority of included studies presented low or unclear risk of bias, but no quality assessment in individual outcomes; [g]: asymmetric funnel plot suggests publication bias; [h]: high level of heterogeneity decreased after subgroup analysis, the results remained unchanged; [i]: substantial heterogeneity ($I^2 > 90\%$) and cannot find the source of heterogeneity; [j]: Newcastle–Ottawa scale used for RCTs; [k]: high risk of bias observed in at least half of studies; [l]: no mention on publication bias, but only include studies published in English or Chinese language; [m]: inadequate to assess due to smaller sample size; neither funding bias was observed nor restriction was set for language, publishing year or country to maximize the extent of the searches; [n]: author judgement; [o]: The $I^2$ in overall studies is 66%, effect size presented significance. Authors did the subgroup analysis and the *p*-value of interaction test for subgroup is 0.01, but no mention of decreasing heterogeneity by subgroup analysis; [p]: approach half studies showed risk of bias; [q]: high risk in domain of blinding of participants and personnel (performance bias); [r]: high-risk bias observed in reporting bias and other bias, unclear in randomization and blinding domains.

**Table 3.** GRADE approach evidence certainty and summary of findings of the surrogate outcomes.

| Author Year | Outcomes | No of Studies | Certainty Assessment | | | | | Certainty | Summary of Findings |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of Bias | Inconsistency | Indirectness | Imprecision | Publication Bias | Overall Certainty of Evidence | Risk Difference with Nutrition Supplements Compared to Placebo (95% CI) |
| **Vitamin D and Analogues** | | | | | | | | | |
| Milajerdi 2019 [39] | CRP or hs-CRP | 5 RCTs | serious [a] | not serious | serious [b] | serious [c] | none | ⊕◯◯◯ VERY LOW | MD **0.41 lower** (0.41 lower to 0.27 higher) |
| Wang 2019 [21] | hs-CRP | 7 RCTs | serious [a] | not serious | serious [b] | not serious | publication bias strongly suspected [d] | ⊕◯◯◯ VERY LOW | MD **0.69 lower** (0.86 lower to 0.53 lower) |
| | IL-6 | 3 RCTs | serious [a] | not serious | serious [b] | not serious | publication bias strongly suspected [d] | ⊕◯◯◯ VERY LOW | MD **0.73 lower** (1.03 lower to 0.44 lower) |
| | TNF-$\alpha$ | 3 RCTs | serious [a] | very serious [e] | serious [b] | not serious | publication bias strongly suspected [d] | ⊕◯◯◯ VERY LOW | MD **56.79 lower** (77.05 lower to 36.52 lower) |
| Zhang 2017 [42] | hs-CRP | 7 RCTs | serious [f] | serious [g] | serious [b] | not serious | none | ⊕◯◯◯ VERY LOW | MD **0.80 lower** (1.26 lower to 0.34 lower) |
| **Dietary Fiber** | | | | | | | | | |
| Wu 2019 [44] | IS | 5 RCTs | serious [h] | not serious [i] | serious [b] | serious [c] | none | ⊕◯◯◯ VERY LOW | MD 0.212 **lower** (2.35 lower to 1.926 higher) |
| | PCS | 7 RCTs | serious [h] | not serious | serious [b] | not serious | none | ⊕⊕◯◯ LOW | MD 16.160 **lower** (23.824 lower to 8.492 lower) |
| **Coenzyme Q10 (CoQ10)** | | | | | | | | | |
| Zhang 2019 [45] | MDA | 2 RCTs | serious [h] | serious [g] | serious [b] | not serious | none | ⊕◯◯◯ VERY LOW | SMD 1.29 **SD lower** (2.32 lower to 0.26 lower) |
| **Probiotics, Prebiotics, Synbiotics** | | | | | | | | | |
| Zheng 2020 [48] | MDA | 4 RCTs | not serious | serious [g] | serious [b] | not serious | none | ⊕⊕◯◯ LOW | SMD 0.79 **SD lower** (1.38 lower to 0.20 lower |
| | CRP | 3 RCTs | not serious | not serious | serious [b] | not serious | none | ⊕⊕⊕◯ MODERATE | SMD 0.71 **SD lower** (1.01 lower to 0.40 lower |
| Jia 2018 [46] | IL-6 | 1 RCT | not serious | not serious | serious [b] | serious [c] | none | ⊕⊕◯◯ LOW | MD 0.23 **lower** (0.27 lower to 0.73 higher) |
| | PCS | 2 RCTs | not serious | serious [g] | serious [b] | not serious | none | ⊕⊕◯◯ LOW | MD 0.70 **lower** (1.4 lower to 0.01 lower) |

The bold of the words in the columns of "summary of findings" means a statistical significance. CI: Confidence interval; CRP: C-reactive protein; hs-CRP: high-sensitivity C-reactive protein; MD: Mean difference; IL-6: interleukin 6; TNF-$\alpha$: tumor necrosis factor-alpha; IS: Indoxyl sulphate; PCS: p-cresyl sulphate; MDA: malondialdehyde; SMD: Standardized mean difference. Explanations: [a]: no data available or no quality assessment available in individual outcomes; [b]: surrogate outcomes for assessment renal protection; [c]: the pooled estimate cannot exclude no effect; [d]: asymmetric funnel plot suggests publication bias; [e]: considerable heterogeneity ($I^2 > 75\%$) and cannot find the source of heterogeneity; [f]: Newcastle–Ottawa scale was used for quality assessment of RCTs; [g]: substantial heterogeneity ($I^2 > 50\%$) and cannot find the source of heterogeneity; [h]: bias observed in randomization or blinding domain, but less than half studies high risk of bias observed in at least half studies; [i]: heterogeneity ($I^2 = 0$, $p = 0.98$) was calculated by ourselves according to the data provided by the original SR author.

**Table 4.** Summary of clinical important outcomes and certainties on the renal protection effect of vitamin D and analogues compared to placebo.

| Author Year/Clinical Important Outcomes | UAER | | UACR | | UPCR | | eGFR | | SCr | | Proteinuria | | Risk of Dialysis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Risk Difference (95% CI) | Certainty | Risk Difference (95% CI) | Certainty | Risk Difference (95% CI) | Certainty | Risk Difference (95% CI) | Certainty | Risk Difference (95% CI) | Certainty | Risk Difference (95% CI) | Certainty | Relative Risk (95%CI) | Certainty |
| **Diabetic Nephropathy** | | | | | | | | | | | | | | |
| Gupta 2019 [26] | **MD −0.39 (−0.71 to −0.07)** | LOW | MD −0.14 (−0.34 to 0.06) | VERY LOW | MD −0.19 (−0.9 to 0.51) | LOW | - | - | - | - | - | - | - | - |
| Wang 2019 [21] | **MD −67.36 (−91.96 to −42.76)** | VERY LOW | - | - | - | - | MD 2.13 (−2.06 to 6.32) | VERY LOW | MD −0.83 (−3.67 to 2.02) | VERY LOW | **MD −0.26 (−0.34 to −0.17)** | LOW | - | - |
| Zhang 2017 [42] | - | - | **MD −0.49 (−0.9 to −0.08)** | LOW | - | - | - | - | SMD −0.16 SD (−0.42 to 0.11) | VERY LOW | **MD −0.23 (−0.3 to −0.15)** | VERY LOW | - | - |
| Derakhshanian 2015 [27] | - | - | MD 17.99 (−35.36 to 71.33) | MODERATE | - | - | - | - | - | - | - | - | - | - |
| Zhao 2014 [41] | - | - | **SMD −0.29 SD (−0.48 to −0.1)** | VERY LOW | - | - | - | - | **MD −0.44 (−0.54 to −0.34)** | VERY LOW | - | - | - | - |
| **Chronic Kidney Disease** | | | | | | | | | | | | | | |
| Xu 2013 [40] | - | - | - | - | - | - | SMD −0.1 SD (−0.24 to 0.03) | LOW | - | - | **Reduced proteinuria: RR [a] 2.00 (1.42 to 2.81)** | MODERATE | 1.48 (0.54 to 4.03) | LOW |

The bold of the words in the context means a statistical significance. [a]: Relative risk (95%CI); UAER: urinary albumin excretion rate; UACR: urine albumin creatinine ratio; UPCR: urine protein creatinine ratio; eGFR: estimated glomerular filtration rate; SCr: serum creatinine; CI: Confidence interval; MD: Mean difference; SMD: Standardized mean difference; RR: Risk ratio.

### 3.4. Omega-3 Polyunsaturated Fatty Acid (PUFA) on Renal Protection

Table 5 showed the effects of omega-3 PUFA on eGFR, progression to ESRD, serum creatinine (SCr), proteinuria and creatinine clearance (CCr) from 2 SRs. In very low to moderate evidence appeared to reduce progression to ESRD significantly and consistently (relative risk, 0.3, 95% CI 0.09 to 0.98 and 0.49, 95% CI 0.24 to 0.99). The effect on reducing proteinuria varied, and the certainty of evidence was low (Table 5).

**Table 5.** Summary of clinical important outcomes and certainties on the renal protection effect of Omega-3 polyunsaturated fatty acid compared to placebo.

| Author Year/Clinical Important Outcomes | eGFR | | Progression to ESKD | | SCr | | Proteinuria | | CCr | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Risk Difference (95% CI) | Certainty | Relative Risk (95% CI) | Certainty | Risk Difference (95% CI) | Certainty | Risk Difference (95% CI) | Certainty | Risk Difference (95% CI) | Certainty |
| Saglimbene 2020 [22] | SMD 0.22 SD (−0.03 to 0.48) | LOW | **RR 0.3 (0.09 to 0.98)** | VERY LOW | MD 2.20 (−17.63 to 22.03) | VERY LOW | MD −0.16 (−0.48 to 0.15) | LOW | - | - |
| Hu 2017 [43] | SMD 0.14 SD (−0.13 to 0.42) | LOW | **RR 0.49 (0.24 to 0.99)** | MODERATE | - | - | **SMD −0.31 SD (−0.53 to −0.10)** | LOW | SMD 0.22 SD (−0.40 to 0.84) | LOW |

The bold of the words in the context means a statistical significance. eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney diseases; SCr: serum creatinine; CCr: creatinine clearance; CI: Confidence interval; MD: Mean difference; SMD: Standardized mean difference; RR: Risk ratio.

### 3.5. Dietary Fiber on Renal Protection

One SR reported two clinical relevant outcome data. Very low certainty evidence suggested that dietary fiber has no effect on Scr or serum urea (Table 2). One SR reported two surrogate outcome data comparing dietary fiber to placebo. Low certainty evidence suggested dietary fiber decreased uremic toxin PCS significantly (1 SR, 7 RCTs, MD −16.16, 95% CI −23.824 to −8.492), but not indoxyl sulphate (IS) (Table 3).

### 3.6. Coenzyme Q10 (CoQ10) on Renal Protection

Very low certainty of evidence suggested CoQ10 decreased MDA significantly (1 SR, 2 RCTs, SMD −1.29 SD, 95% CI −2.32 to −0.26) (Table 3), but no effect on clinically important outcomes, SCr and serum urea (Table 2).

### 3.7. Probiotics, Prebiotics and Synbiotics on Renal Protection

Table 6 shows the effect of biotics on serum urea, BUN, and SCr. Three SRs suggested biotics effects on serum urea varied; however, significant decrease serum urea compared to placebo (low certainty: MD −2.12 mmol/L, 95% CI −3.86 to −0.37; moderate certainty: MD −5.0 mmol/L, 95% CI −9.45 to −0.54) with low to moderate certainty evidence. Very low certainty of evidence suggested biotics did not affect BUN and SCr.

**Table 6.** Summary of clinical important outcomes and certainties on the renal protection effect of biotics compared to placebo.

| Author Year/Clinical Important Outcomes | Serum Urea | | BUN | | SCr | |
| --- | --- | --- | --- | --- | --- | --- |
| | Risk Difference (95% CI) | Certainty | Risk Difference (95% CI) | Certainty | Risk Difference (95% CI) | Certainty |
| McFarlane 2019 [25] | **MD −2.12 [a] (−3.86 to −0.37)** | LOW | - | - | - | - |
| Tao 2019 [47] | **MD −30.01 [b] (−56.78 to −3.25)** | MODERATE | - | - | - | - |
| Jia 2018 [46] | - | - | MD −5.78 (−21.42 to 9.86) | VERY LOW | MD 0.10 (−0.11 to 0.31) | VERY LOW |
| Pisano 2018 [23] | SMD −0.20 SD (−0.41 to 0.01) | VERY LOW | - | - | MD −0.02 (−0.09 to 0.05) | VERY LOW |

The bold of the words in the context means a statistical significance. [a]: the unit is mmol/L; [b]: the unit is mg/dL, conversion to SI unit is MD −5.00 (−9.45 to −0.54); BUN: blood urea nitrogen, SCr: serum creatinine; CI: Confidence interval; MD: Mean difference; SMD: Standardized mean difference.

Low to moderate certainty evidence suggested biotics decreased MDA, CRP and PCS significantly (MDA: 1 SR, 4 RCTs, SMD –0.79 SD, 95% CI −1.38 to −0.20; CRP: 1 SR, 3 RCTs, SMD –0.71 SD, 95% CI −1.01 to −0.40; PCS: 1 SR, 2 RCTs, MD −0.70, 95% CI −1.4 to −0.01), but no effect on IL-6 (Table 3).

This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

## 4. Discussion

SRs through the GRADE approach recommended by the Cochrane Collaboration provides rating and strengthening the quality of evidence and has been increasingly adopted by researchers worldwide. The GRADE approach divides the quality of SRs into four evidence levels. For example, the high evidence is reliable without side effects; the moderate or low evidence is needed to consult physicians; and, the very low evidence is not recommended. In this SR and meta-analysis, we adopted the GRADE approach to evaluate the beneficial effects of nutrition supplements on CKD prevention. Our findings provided that evidence of the beneficial effects of those nutrition supplements in CKD patients mostly seems to be low to very low evidence on proteinuria, kidney function, and inflammations. Thus, it is recommended in CKD patients to consult physicians for the prescription of nutrition supplements.

### 4.1. Findings and Implications of this Systematic Review

Vitamin D, including vitamin D2 and vitamin D3, is available for over-the-counter purchase and responsible for increasing intestinal absorption of calcium and phosphate and multiple biological effects [49]. Vitamin D3 is the type that most experts recommend to be utilized in clinical practice because of the more stable and potent form [50]. A review of observational studies has shown associations between vitamin D deficiency and risk of CKD, cardiovascular diseases, cancer, diabetes, infectious diseases, and death [49,51]. This study pooled the results of seven SRs that addressed the effects of vitamin D and analogues administered to patients with proteinuria and renal dysfunction. Data of two SRs show that vitamin D and analogues supplementation in patients with diabetes could reduce proteinuria but not affect kidney function [21,52]; however, other SR data show the contrary results of proteinuria protection [26,27]. Furthermore, most results from SRs suggested no effects on kidney function after receiving vitamin D and analogues in diabetes patients [21,52] and CKD patients [40]. Moreover, there is very low evidence that vitamin D and analogues supplements maybe decreased the inflammatory markers of hs-CRP, IL-6, and TNF-$\alpha$. Through GRADE approach, our results showed that the beneficial effects of receiving vitamin D and analogues seem smaller in diabetes patients, and the certainty of the evidence was low to very low on proteinuria and very low on kidney function and inflammations. In CKD patients, the beneficial effects of vitamin D and analogues supplements were moderate evidence of proteinuria and low evidence of kidney function. Thus, consistent evidence showed vitamin D and analogues decreased the risk of proteinuria and/or UAER in diabetic nephropathy and CKD, but the strength of the evidence is mostly limited by the quality of the individual studies. It is recommended to discuss with a physician before deciding to receive vitamin D and analogues.

Omega-3 PUFA, a class of particular fatty acids with many biological functions, has been reported to or used together with diet and exercise to help lower triglyceride levels in the blood [53]. Reviews of clinical and epidemiological studies have shown the beneficial effects of omega-3 PUFAs supplements on a series of illnesses such as coronary artery disease and heart failure [54], stroke [55], metabolic syndrome [56], and neurodegenerative diseases (Parkinson's and Alzheimer's diseases) [57]. Apart from these disorders, there have been found lower levels of serum Omega-3 PUFA in patients with advanced CKD compared with the general population probably due to malabsorption, metabolic changes, and Omega-3 PUFA loss during the dialysis process [58–60]. Additionally, Omega-3 PUFA defi-

ciency is independently related to cardiovascular disease in advanced CKD patients [61,62]. In CKD patients without receiving dialysis, Omega-3 PUFA intake may lower the risk of developing end-stage kidney disease [22,43] and cardiovascular deaths [22]. The possible causes have been reported from the pleiotropic effects of Omega-3 PUFA, including reducing blood pressure levels, lessening inflammation, and improving endothelial function, and altering platelet function and blood viscosity [63–66]. Via using GRADE approach, our data showed that the moderate to very low evidence appeared to reduce progression to ESRD (relative risk, 0.3, 95% CI 0.09 to 0.98 and 0.49, 95% CI 0.24 to 0.99). Moreover, the effect on reducing proteinuria varied, and the certainty of the evidence was low. Due to the inconsistency of variable evidence in different studies on the eGFR, SCr, proteinuria, or CCr, the recommendation of Omega-3 PUFA supplements needs to consider the benefits over the adverse effects in CKD patients after discussing with physicians.

Higher dietary fiber and lower dietary acid loads (e.g., more fruits and vegetables and fewer meats and cheeses) have been reported to reduce the risk of CKD progression [19,20,24]. A meta-analysis of 14 trials involving 143 CKD patients showed the association of higher dietary fiber intake and lower serum urea and SCr levels (MD −1.76 mmol/l, 95% CI −3.00 to −0.51 and MD −22.83 mmol/l, 95% CI −42.63 to −3.02, respectively) [24]; however, the certainty of evidence is at the very low level because of risk of bias and imprecision form analysis of the GRADE approach. Another meta-analysis of 203 CKD patients, showed that dietary fiber decreased uremic toxin PCS levels (MD –16.16, 95% CI −23.824 to −8.492) [44], which also was low certainty of evidence due to small sample size and risks from some data bias and indirectness. In this study, the data showed very low certainty evidence that dietary fiber has no effect on Scr or serum urea. Furthermore, low certainty evidence suggested dietary fiber decreased uremic toxin PCS levels significantly, but did not affect IS levels. Thus, limited evidence showed that dietary fiber intake might reduce the uremic toxins such as serum urea, SCr, and PCS levels, but there is not found any effect on clinically important outcomes. The evidence is insufficient to recommend dietary fiber for kidney protection in CKD patients.

CoQ10, first identified in 1940, is mostly found in meat, fish, and whole grains [67]. CoQ10 generate adenosine triphosphate (ATP) energy to cell [67] and is most commonly used for an antioxidant that helps improve cardiovascular diseases [68,69], heart failure [70], diabetes [71], hypercholesterolemia [72], migraine headache [73], and many other conditions related to lower CoQ10 levels. Furthermore, CoQ10 has been reported to play an essential role in blood metabolic profiles in diabetic kidney disease [45], which indicates lower blood sugar, blood lipid, and MDA levels, but no effect on serum urea and SCr. By using the GRADE approach, this study further showed the very low certainty of evidence on blood metabolic profiles and no impact on kidney function. Thus, CoQ10 intake is insufficiently evident to recommend in CKD patients.

Microbiota dysbiosis is closely associated with many diseases related to chronic inflammations, including obesity, diabetes, cardiovascular diseases, non-alcoholic fatty liver disease, and obesity-induced CKD [74–76]. So far, the prescribed prebiotics, probiotics, and synbiotics may show an impact on the amelioration of these diseases [77,78]. However, the safety issue on these biotics supplements is most important, due to the trend of the broad use of these biotics under different clinical circumstances. There have been reported in a few situations of bacteremia, sepsis, fungal infection, or endocarditis following biotics intake, especially for some immunocompromised patients, malnutrition, or suffering from cancer [79–81]. In this study, we investigated the effect of biotics on serum urea, BUN, and SCr, and some metabolic profiles such as MDA, CRP, and PCS in CKD patients. Four SRs showed biotics effects on serum urea were inconsistent results and at very low to moderate certainty of evidence due to the risk of data bias and imprecision [23,25,46,47]. Additionally, the biotics intake appeared to decrease MDA, CRP, and PCS levels significantly [46,48]. However, biotics intake did not affect SCr levels in CKD patients [23,46], which was at the very low certainty of the evidence. Thus, biotics supplements seemed only to reduce serum

urea and some metabolic profiles in CKD patients. We suggest CKD patients discuss with a physician before considering biotics supplements.

*4.2. Strengths, Limitations and Further Research Needs*

In summary, this study was the first and composed of seven SRs of vitamin D and analogues, two SRs of omega-3 PUFA, two SRs of dietary fiber, one SR of CoQ10, and five SRs of biotics for effect on proteinuria, kidney function, and inflammation in CKD patients. According to the GRADE approach assessment, the strength of evidence was low to very low levels for the benefits of these nutrition supplements on proteinuria and kidney function and did not appear to improve CKD prognosis. The recommendation of these nutrition supplements in CKD patients needs to discuss with physicians and consider the benefits over the adverse effects. Multicenter and large samples of RCTs with more than ten years of follow-up merit to be conducted in the future and to verify the benefits of nutrition supplements in CKD patients.

## Abbreviations

| | |
|---|---|
| BUN | blood urea nitrogen |
| CCr | creatinine clearance |
| CI | confidence interval |
| CKD | chronic kidney disease |
| CoQ10 | coenzyme Q10 |
| CRP | C-reactive protein |
| DN | diabetic nephropathy |
| eGFR | estimated glomerular filtration rate |
| ESKD | end stage kidney disease |
| ESRD | end-stage renal disease |
| GRADE | Grading of Recommendations Assessment, Development, and Evaluation |
| hs-CRP | high-sensitivity C-reactive protein |
| IL-6 | interleukin 6 |
| IS | indoxyl sulphate |
| MD | mean difference |
| MDA | malondialdehyde |
| OIS | optimal information size |
| PCS | p-cresyl sulphate |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PUFA | polyunsaturated fatty acid |
| RCTs | randomized-controlled trials |
| RoB | risk of bias |

| RR | risk ratio |
|---|---|
| SCr | serum creatinine |
| SMD | standardized mean difference |
| SR | systematic review |
| T1DN | type 1 diabetic nephtopathy |
| T2DN | type 2 diabetic nephtopathy |
| TNF-$\alpha$ | tumor necrosis factor-alpha |
| UACR | urine albumin creatinine ratio |
| UAER | urinary albumin excretion rate |
| UPCR | urine protein creatinine ratio |

## References

1. Van Dijk, P.C.; Jager, K.J.; Stengel, B.; Gronhagen-Riska, C.; Feest, T.G.; Briggs, J.D. Renal replacement therapy for diabetic end-stage renal disease: Data from 10 registries in Europe (1991–2000). *Kidney Int.* **2005**, *67*, 1489–1499. [CrossRef] [PubMed]
2. Robinson, B.M.; Akizawa, T.; Jager, K.J.; Kerr, P.G.; Saran, R.; Pisoni, R.L. Factors affecting outcomes in patients reaching end-stage kidney disease worldwide: Differences in access to renal replacement therapy, modality use, and haemodialysis practices. *Lancet* **2016**, *388*, 294–306. [CrossRef]
3. Caskey, F.J.; Kramer, A.; Elliott, R.F.; Stel, V.S.; Covic, A.; Cusumano, A.; Geue, C.; Macleod, A.M.; Zwinderman, A.H.; Stengel, B.; et al. Global variation in renal replacement therapy for end-stage renal disease. *Nephrol. Dial. Transplant.* **2011**, *26*, 2604–2610. [CrossRef] [PubMed]
4. Ritz, E.; Orth, S.R. Nephropathy in patients with type 2 diabetes mellitus. *N. Engl. J. Med.* **1999**, *341*, 1127–1133. [CrossRef] [PubMed]
5. Peralta, C.A.; Norris, K.C.; Li, S.; Chang, T.I.; Tamura, M.K.; Jolly, S.E.; Bakris, G.; McCullough, P.A.; Shlipak, M.; KEEP investigators. Blood pressure components and end-stage renal disease in persons with chronic kidney disease: The Kidney Early Evaluation Program (KEEP). *Arch. Intern. Med.* **2012**, *172*, 41–47. [CrossRef]
6. Stefansson, V.T.N.; Schei, J.; Solbu, M.D.; Jenssen, T.G.; Melsom, T.; Eriksen, B.O. Metabolic syndrome but not obesity measures are risk factors for accelerated age-related glomerular filtration rate decline in the general population. *Kidney Int.* **2018**, *93*, 1183–1190. [CrossRef]
7. Jha, V.; Garcia-Garcia, G.; Iseki, K.; Li, Z.; Naicker, S.; Plattner, B.; Saran, R.; Wang, A.Y.M.; Yang, C.W. Chronic kidney disease: Global dimension and perspectives. *Lancet* **2013**, *382*, 260–272. [CrossRef]
8. Go, A.S.; Chertow, G.M.; Fan, D.; McCulloch, C.E.; Hsu, C.Y. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N. Engl. J. Med.* **2004**, *351*, 1296–1305. [CrossRef]
9. Matsushita, K.; Coresh, J.; Sang, Y.; Chalmers, J.; Fox, C.; Guallar, E.; Jafar, T.; Jassal, S.K.; Landman, G.W.D.; Muntner, P.; et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: A collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol.* **2015**, *3*, 514–525. [CrossRef]
10. Astor, B.C.; Matsushita, K.; Gansevoort, R.T.; van der Velde, M.; Woodward, M.; Levey, A.S.; Jong, P.E.; Coresh, J.; Astor, B.C.; Matsushita, K. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int.* **2011**, *79*, 1331–1340. [CrossRef]
11. Inker, L.A.; Grams, M.E.; Levey, A.S.; Coresh, J.; Cirillo, M.; Gansevoort, R.T.; Gutierriz, O.M.; Hamano, T.; Heine, G.H.; Ishikawa, S.; et al. Relationship of Estimated GFR and Albuminuria to Concurrent Laboratory Abnormalities: An Individual Participant Data Meta-analysis in a Global Consortium. *Am. J. Kidney Dis.* **2019**, *73*, 206–217. [CrossRef] [PubMed]
12. Provenzano, M.; Andreucci, M.; De Nicola, L.; Garofalo, C.; Battaglia, Y.; Borrelli, S.; Gagliardi, I.; Faga, T.; Michael, A.; Mastroroberto, P.; et al. The role of prognostic and predictive biomarkers for assessing cardiovascular risk in chronic kidney disease patients. *BioMed Res. Int.* **2020**, 2314128. [CrossRef] [PubMed]
13. Klahr, S.; Levey, A.S.; Beck, G.J.; Caggiula, A.W.; Hunsicker, L.; Kusek, J.W.; Striker, G. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N. Engl. J. Med.* **1994**, *330*, 877–884. [CrossRef] [PubMed]
14. Menon, V.; Kopple, J.D.; Wang, X.; Beck, G.J.; Collins, A.J.; Kusek, J.W.; Greene, T.; Levey, A.S.; Sarnak, M.J. Effect of a very low-protein diet on outcomes: Long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. *Am. J. Kidney Dis.* **2009**, *53*, 208–217. [CrossRef] [PubMed]
15. Rosman, J.B.; ter Wee, P.M.; Meijer, S.; Piers-Becht, T.P.; Sluiter, W.J.; Donker, A.J. Prospective randomised trial of early dietary protein restriction in chronic renal failure. *Lancet* **1984**, *2*, 1291–1296. [CrossRef]
16. Hansen, H.P.; Christensen, P.K.; Tauber-Lassen, E.; Klausen, A.; Jensen, B.R.; Parving, H.H. Low-protein diet and kidney function in insulin-dependent diabetic patients with diabetic nephropathy. *Kidney Int.* **1999**, *55*, 621–628. [CrossRef]
17. Hansen, H.P.; Tauber-Lassen, E.; Jensen, B.R.; Parving, H.H. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. *Kidney Int.* **2002**, *62*, 220–228. [CrossRef]
18. De Borst, M.H.; Hajhosseiny, R.; Tamez, H.; Wenger, J.; Thadhani, R.; Goldsmith, D.J.A. Active vitamin D treatment for reduction of residual proteinuria: A systematic review. *J. Am. Soc. Nephrol.* **2013**, *24*, 1863–1871. [CrossRef]

19. Goraya, N.; Simoni, J.; Jo, C.; Wesson, D.E. Dietary acid reduction with fruits and vegetables or bicarbonate attenuates kidney injury in patients with a moderately reduced glomerular filtration rate due to hypertensive nephropathy. *Kidney Int.* **2012**, *81*, 86–93. [CrossRef]

20. Banerjee, T.; Crews, D.C.; Wesson, D.E.; Tilea, A.M.; Saran, R.; Ríos-Burrows, N.; Williams, D.E.; Powe, N.R.; Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. High Dietary Acid Load Predicts ESRD among Adults with CKD. *J. Am. Soc. Nephrol.* **2015**, *26*, 1693–1700. [CrossRef]

21. Wang, Y.; Yang, S.; Zhou, Q.; Zhang, H.; Yi, B. Effects of Vitamin D Supplementation on Renal Function, Inflammation and Glycemic Control in Patients with Diabetic Nephropathy, a Systematic Review and Meta-Analysis. *Kidney Blood Press. Res.* **2019**, *44*, 72–87. [CrossRef] [PubMed]

22. Saglimbene, V.M.; Wong, G.; van Zwieten, A.; Palmer, S.C.; Ruospo, M.; Natale, P.; Campbell, K.; Teixeira-Pinto, A.; Craig, J.C.; Strippoli, G.F.M. Effects of omega-3 polyunsaturated fatty acid intake in patients with chronic kidney disease: Systematic review and meta-analysis of randomized controlled trials. *Clin. Nutr.* **2020**, *39*, 358–368. [CrossRef] [PubMed]

23. Pisano, A.; D'Arrigo, G.; Coppolino, G.; Bolignano, D. Biotic Supplements for Renal Patients: A Systematic Review and Meta-Analysis. *Nutrients* **2018**, *10*, 1224. [CrossRef] [PubMed]

24. Chiavaroli, L.; Mirrahimi, A.; Sievenpiper, J.L.; Jenkins, D.J.; Darling, P.B. Dietary fiber effects in chronic kidney disease: A systematic review and meta-analysis of controlled feeding trials. *Eur. J. Clin. Nutr.* **2015**, *69*, 761–768. [CrossRef]

25. McFarlane, C.; Ramos, C.I.; Johnson, D.W.; Campbell, K.L. Prebiotic, Probiotic, and Synbiotic Supplementation in Chronic Kidney Disease: A Systematic Review and Meta-analysis. *J. Ren. Nutr.* **2019**, *29*, 209–220. [CrossRef]

26. Gupta, S.; Goyal, P.; Feinn, R.S.; Mattana, J. Role of Vitamin D and Its Analogues in Diabetic Nephropathy: A Meta-analysis. *Am. J. Med Sci.* **2019**, *357*, 223–229. [CrossRef]

27. Derakhshanian, H.; Shab-Bidar, S.; Speakman, J.R.; Nadimi, H.; Djafarian, K. Vitamin D and diabetic nephropathy: A systematic review and meta-analysis. *Nutrition* **2015**, *31*, 1189–1194. [CrossRef]

28. Moher, D.; Liberati, A.; Tetzlaff, J.; Tetzlaff, J.; Altman, D.G.; Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Ann. Intern. Med.* **2009**, *151*, 264–269. [CrossRef]

29. Lin, P.C.S.Y.; Hung, P.L.; Tu, S.C. Precision searching: An innovative search strategy for retrieving the newest and optimal systematic reviews from PubMed. Advances in Evidence Synthesis: Special issue. *Cochrane Database Syst. Rev.* **2020**, *9* (Suppl. 1), 311. [CrossRef]

30. Higgins, J.P.T.; Thomas, J.; Chandler, J.; Cumpston, M.; Li, T.; Page, M.J.; Welch, V.A. (Eds.) *Cochrane Handbook for Systematic Reviews of Interventions*; Version 6.0; Updated July 2019; Cochrane: London, UK, 2019.

31. Schünemann, H.J.; Mustafa, R.A.; Brozek, J.; Steingart, K.R.; Leeflang, M.; Murad, M.H.; Bossuyt, P.; Glasziou, P.; Jaeschke, R.; Lange, S.; et al. GRADE guidelines: 21 part 2. Test accuracy: Inconsistency, imprecision, publication bias, and other domains for rating the certainty of evidence and presenting it in evidence profiles and summary of findings tables. *J. Clin. Epidemiol.* **2020**, *122*, 142–152. [CrossRef]

32. Schünemann, H.J.; Mustafa, R.A.; Brozek, J.; Steingart, K.R.; Leeflang, M.; Murad, M.H.; Bossuyt, P.; Glasziou, P.; Jaeschke, R.; Lange, S.; et al. GRADE guidelines: 21 part 1. Study design, risk of bias, and indirectness in rating the certainty across a body of evidence for test accuracy. *J. Clin. Epidemiol.* **2020**, *122*, 129–141. [CrossRef] [PubMed]

33. Guyatt, G.H.; Oxman, A.D.; Kunz, R.; Brozek, J.; Alonso-Coello, P.; Rind, D.; Devereaux, P.J.; Montori, V.M.; Freyschuss, B.; Vist, G.; et al. GRADE guidelines 6. Rating the quality of evidence—Imprecision. *J. Clin. Epidemiol.* **2011**, *64*, 1283–1293. [CrossRef] [PubMed]

34. Guyatt, G.H.; Oxman, A.D.; Kunz, R.; Woodcock, J.; Brozek, J.; Helfand, M.; Alonso-Coello, P.; Falck-Ytter, Y.; Jaeschke, R.; Vist, G.; et al. GRADE guidelines: 8. Rating the quality of evidence—Indirectness. *J. Clin. Epidemiol.* **2011**, *64*, 1303–1310. [CrossRef] [PubMed]

35. Guyatt, G.H.; Oxman, A.D.; Kunz, R.; Woodcock, J.; Brozek, J.; Helfand, M.; Alonso-Coello, P.; Glasziou, P.; Jaeschke, R.; Akl, E.A.; et al. GRADE guidelines: 7. Rating the quality of evidence—Inconsistency. *J. Clin. Epidemiol.* **2011**, *64*, 1294–1302. [CrossRef] [PubMed]

36. Guyatt, G.H.; Oxman, A.D.; Montori, V.; Vist, G.; Kunz, R.; Brozek, J.; Alonso-Coello, P.; Djulbegovic, B.; Atkins, D.; Falck-Ytter, Y.; et al. GRADE guidelines: 5. Rating the quality of evidence—Publication bias. *J. Clin. Epidemiol.* **2011**, *64*, 1277–1282. [CrossRef]

37. Guyatt, G.H.; Oxman, A.D.; Vist, G.; Kunz, R.; Brozek, J.; Alonso-Coello, P.; Montori, V.; Akl, E.A.; Djulbegovic, B.; Falck-Ytter, Y.; et al. GRADE guidelines: 4. Rating the quality of evidence—Study limitations (risk of bias). *J. Clin. Epidemiol.* **2011**, *64*, 407–415. [CrossRef]

38. Ellis, P.D. *The Essential Guide to Effect Sizes: Statistical Power, Meta-Analysis, and the Interpretation of Research Results*, 1st ed.; Cambridge University Press: Cambridge, UK, 2010.

39. Milajerdi, A.; Ostadmohammadi, V.; Amirjani, S.; Kolahdooz, F.; Asemi, Z. The effects of vitamin D treatment on glycemic control, serum lipid profiles, and C-reactive protein in patients with chronic kidney disease: A systematic review and meta-analysis of randomized controlled trials. *Int. Urol. Nephrol.* **2019**, *51*, 1567–1580. [CrossRef]

40. Xu, L.; Wan, X.; Huang, Z.; Zeng, F.; Wei, G.; Fang, D.; Deng, W.; Li, Y. Impact of vitamin D on chronic kidney diseases in non-dialysis patients: A meta-analysis of randomized controlled trials. *PLoS ONE* **2013**, *8*, e61387. [CrossRef]

41. Zhao, J.Y.; Dong, J.J.; Wang, H.P.; Shang, H.X.; Zhang, D.M.; Liao, L. Efficacy and safety of vitamin D3 in patients with diabetic nephropathy: A meta-analysis of randomized controlled trials. *Chin. Med. J.* **2014**, *127*, 2837–2843.

42. Zhang, M.; Liu, T.; Li, W.; Gong, W.; Yang, X.; Xi, J. Efficacy of Vitamin D3 in Patients With Diabetic Nephropathy: An Updated Meta-Analysis. *Iran. Red Crescent Med. J.* **2017**, *19*, e64275. [CrossRef]

43. Hu, J.; Liu, Z.; Zhang, H. Omega-3 fatty acid supplementation as an adjunctive therapy in the treatment of chronic kidney disease: A meta-analysis. *Clinics (Sao Paulo)* **2017**, *72*, 58–64. [CrossRef]

44. Wu, M.; Cai, X.; Lin, J.; Zhang, X.; Scott, E.M.; Li, X. Association between fibre intake and indoxyl sulphate/P-cresyl sulphate in patients with chronic kidney disease: Meta-analysis and systematic review of experimental studies. *Clin. Nutr.* **2019**, *38*, 2016–2022. [CrossRef] [PubMed]

45. Zhang, X.; Shi, Z.; Liu, Q.; Quan, H.; Cheng, X. Effects of coenzyme Q10 intervention on diabetic kidney disease: A systematic review and meta-analysis. *Medicine (Baltimore)* **2019**, *98*, e15850. [CrossRef] [PubMed]

46. Jia, L.; Jia, Q.; Yang, J.; Jia, R.; Zhang, H. Efficacy of Probiotics Supplementation On Chronic Kidney Disease: A Systematic Review and Meta-Analysis. *Kidney Blood Press. Res.* **2018**, *43*, 1623–1635. [CrossRef] [PubMed]

47. Tao, S.; Tao, S.; Cheng, Y.; Liu, J.; Ma, L.; Fu, P. Effects of probiotic supplements on the progression of chronic kidney disease: A meta-analysis. *Nephrology (Carlton)* **2019**, *24*, 1122–1130. [CrossRef] [PubMed]

48. Zheng, H.J.; Guo, J.; Wang, Q.; Wang, L.; Wang, Y.; Zhang, F.; Huang, W.J.; Zhang, W.; Liu, W.J.; Wang, Y. Probiotics, prebiotics, and synbiotics for the improvement of metabolic profiles in patients with chronic kidney disease: A systematic review and meta-analysis of randomized controlled trials. *Crit. Rev. Food Sci. Nutr.* **2021**, *61*, 577–598. [CrossRef]

49. Holick, M.F. Vitamin D deficiency. *N. Engl. J. Med.* **2007**, *357*, 266–281. [CrossRef]

50. Wolpowitz, D.; Gilchrest, B.A. The vitamin D questions: How much do you need and how should you get it? *J. Am. Acad. Dermatol.* **2006**, *54*, 301–317. [CrossRef]

51. Autier, P.; Boniol, M.; Pizot, C.; Mullie, P. Vitamin D status and ill health: A systematic review. *Lancet Diabetes Endocrinol.* **2014**, *2*, 76–89. [CrossRef]

52. Zhang, M.; Zhao, L.J.; Zhou, Y.; Badr, R.; Watson, P.; Ye, A.; Zhou, B.; Zhang, J.; Deng, H.W.; Recker, R.R.; et al. SNP rs11185644 of RXRA gene is identified for dose-response variability to vitamin D3 supplementation: A randomized clinical trial. *Sci. Rep.* **2017**, *7*, 40593. [CrossRef]

53. Sahebkar, A.; Simental-Mendia, L.E.; Mikhailidis, D.P.; Pirro, M.; Banach, M.; Sirtori, C.R.; Reiner, Z. Effect of omega-3 supplements on plasma apolipoprotein C-III concentrations: A systematic review and meta-analysis of randomized controlled trials. *Ann. Med.* **2018**, *50*, 565–575. [CrossRef] [PubMed]

54. Lavie, C.J.; Milani, R.V.; Mehra, M.R.; Ventura, H.O. Omega-3 polyunsaturated fatty acids and cardiovascular diseases. *J. Am. Coll. Cardiol.* **2009**, *54*, 585–594. [CrossRef] [PubMed]

55. Saber, H.; Yakoob, M.Y.; Shi, P.; Longstreth, W.T., Jr.; Lemaitre, R.N.; Siscovick, D.; Rexrode, K.M.; Willett, W.C.; Mozaffarian, D. Omega-3 Fatty Acids and Incident Ischemic Stroke and Its Atherothrombotic and Cardioembolic Subtypes in 3 US Cohorts. *Stroke* **2017**, *48*, 2678–2685. [CrossRef] [PubMed]

56. Jang, H.; Park, K. Omega-3 and omega-6 polyunsaturated fatty acids and metabolic syndrome: A systematic review and meta-analysis. *Clin. Nutr.* **2020**, *39*, 765–773. [CrossRef]

57. Zhuang, Z.; Wang, Z.H.; Huang, Y.Y.; Zheng, Q.; Pan, X.D. Protective effect and possible mechanisms of ligustrazine isolated from Ligusticum wallichii on nephropathy in rats with diabetes: A preclinical systematic review and meta-analysis. *J. Ethnopharmacol.* **2020**, *252*, 112568. [CrossRef]

58. Friedman, A.N.; Moe, S.M.; Perkins, S.M.; Li, Y.; Watkins, B.A. Fish consumption and omega-3 fatty acid status and determinants in long-term hemodialysis. *Am. J. Kidney Dis.* **2006**, *47*, 1064–1071. [CrossRef]

59. Friedman, A.N.; Yu, Z.; Tabbey, R.; Denski, C.; Tamez, H.; Wenger, J.; Thadhani, R.; Li, Y.; Watkins, B.A. Low blood levels of long-chain n-3 polyunsaturated fatty acids in US hemodialysis patients: Clinical implications. *Am. J. Nephrol.* **2012**, *36*, 451–458. [CrossRef]

60. Saglimbene, V.M.; Wong, G.; Ruospo, M.; Palmer, S.C.; Campbell, K.; Larsen, V.G.; Natale, P.; Teixeira-Pinto, A.; Carrero, J.J.; Stenvinkel, P.; et al. Dietary n-3 polyunsaturated fatty acid intake and all-cause and cardiovascular mortality in adults on hemodialysis: The DIET-HD multinational cohort study. *Clin. Nutr.* **2019**, *38*, 429–437. [CrossRef]

61. Shoji, T.; Kakiya, R.; Hayashi, T.; Tsujimoto, Y.; Sonoda, M.; Shima, H.; Mori, K.; Fukumoto, S.; Tahara, H.; Shioi, A.; et al. Serum n-3 and n-6 polyunsaturated fatty acid profile as an independent predictor of cardiovascular events in hemodialysis patients. *Am. J. Kidney Dis.* **2013**, *62*, 568–576. [CrossRef]

62. Friedman, A.N.; Yu, Z.; Tabbey, R.; Denski, C.; Tamez, H.; Wenger, J.; Thadhani, R.; Li, Y.; Watkins, B.A. Inverse relationship between long-chain n-3 fatty acids and risk of sudden cardiac death in patients starting hemodialysis. *Kidney Int.* **2013**, *83*, 1130–1135. [CrossRef]

63. Thies, F.; Garry, J.M.; Yaqoob, P.; Rerkasem, K.; Williams, J.; Shearman, C.P.; Gallagher, P.J.; Calder, P.C.; Grimble, R.F. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: A randomised controlled trial. *Lancet* **2003**, *361*, 477–485. [CrossRef]

64. Miyajima, T.; Tsujino, T.; Saito, K.; Yokoyama, M. Effects of eicosapentaenoic acid on blood pressure, cell membrane fatty acids, and intracellular sodium concentration in essential hypertension. *Hypertens Res.* **2001**, *24*, 537–542. [CrossRef] [PubMed]

65. Mori, T.A.; Beilin, L.J. Omega-3 fatty acids and inflammation. *Curr. Atheroscler. Rep.* **2004**, *6*, 461–467. [CrossRef] [PubMed]

66.  Terano, T.; Hirai, A.; Hamazaki, T.; Kobayashi, S.; Fujita, T.; Tamura, Y.; Kumagai, A. Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity and red cell deformability in healthy human subjects. *Atherosclerosis* **1983**, *46*, 321–331. [CrossRef]

67.  Saini, R. Coenzyme Q10: The essential nutrient. *J. Pharm. Bioallied Sci.* **2011**, *3*, 466–467. [CrossRef] [PubMed]

68.  Ayers, J.; Cook, J.; Koenig, R.A.; Sisson, E.M.; Dixon, D.L. Recent Developments in the Role of Coenzyme Q10 for Coronary Heart Disease: A Systematic Review. *Curr. Atheroscler. Rep.* **2018**, *20*, 29. [CrossRef]

69.  Flowers, N.; Hartley, L.; Todkill, D.; Strangers, S.; Rees, K. Co-enzyme Q10 supplementation for the primary prevention of cardiovascular disease. *Cochrane Database Syst. Rev.* **2014**, CD010405. [CrossRef]

70.  Sharma, A.; Fonarow, G.C.; Butler, J.; Ezekowitz, J.A.; Felker, G.M. Coenzyme Q10 and Heart Failure: A State-of-the-Art Review. *Circ. Heart Fail.* **2016**, *9*, e002639. [CrossRef]

71.  Zhang, S.Y.; Yang, K.L.; Zeng, L.T.; Wu, X.H.; Huang, H.Y. Effectiveness of Coenzyme Q10 Supplementation for Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Int. J. Endocrinol.* **2018**, *2018*, 6484839. [CrossRef]

72.  Pirro, M.; Mannarino, M.R.; Bianconi, V.; Simental-Mendia, L.E.; Bagaglia, F.; Mannarino, E.; Sahebkar, A. The effects of a nutraceutical combination on plasma lipids and glucose: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol. Res.* **2016**, *110*, 76–88. [CrossRef]

73.  Parohan, M.; Sarraf, P.; Javanbakht, M.H.; Ranji-Burachaloo, S.; Djalali, M. Effect of coenzyme Q10 supplementation on clinical features of migraine: A systematic review and dose-response meta-analysis of randomized controlled trials. *Nutr. Neurosci.* **2019**, *23*, 868–875. [CrossRef] [PubMed]

74.  Boulange, C.L.; Neves, A.L.; Chilloux, J.; Nicholson, J.K.; Dumas, M.E. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. *Genome Med.* **2016**, *8*, 42. [CrossRef] [PubMed]

75.  Ley, R.E.; Turnbaugh, P.J.; Klein, S.; Gordon, J.I. Microbial ecology: Human gut microbes associated with obesity. *Nature* **2006**, *444*, 1022–1023. [CrossRef] [PubMed]

76.  Saez-Lara, M.J.; Robles-Sanchez, C.; Ruiz-Ojeda, F.J.; Plaza-Diaz, J.; Gil, A. Effects of Probiotics and Synbiotics on Obesity, Insulin Resistance Syndrome, Type 2 Diabetes and Non-Alcoholic Fatty Liver Disease: A Review of Human Clinical Trials. *Int. J. Mol. Sci.* **2016**, *17*, 928. [CrossRef]

77.  Chang, C.J.; Lin, T.L.; Tsai, Y.L.; Wu, T.R.; Lai, W.F.; Lu, C.C.; Lai, H.C. Next generation probiotics in disease amelioration. *J. Food Drug Anal.* **2019**, *27*, 615–622. [CrossRef]

78.  Tsai, Y.L.; Lin, T.L.; Chang, C.J.; Wu, T.R.; Lai, W.F.; Lu, C.C.; Lai, H.C. Probiotics, prebiotics and amelioration of diseases. *J. Biomed. Sci.* **2019**, *26*, 3. [CrossRef]

79.  Doron, S.; Snydman, D.R. Risk and safety of probiotics. *Clin. Infect. Dis.* **2015**, *60* (Suppl. 2), S129–S134. [CrossRef]

80.  Boyle, R.J.; Tang, M.L. The role of probiotics in the management of allergic disease. *Clin. Exp. Allergy* **2006**, *36*, 568–576. [CrossRef]

81.  Hemarajata, P.; Versalovic, J. Effects of probiotics on gut microbiota: Mechanisms of intestinal immunomodulation and neuro-modulation. *Therap. Adv. Gastroenterol.* **2013**, *6*, 39–51. [CrossRef]