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Meta-analyses

Effects of soy protein containing isoflavones in patients with chronic kidney disease: A systematic review and meta-analysis

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SUMMARY

Background & aims: Recent studies have demonstrated mixed results on the effects of soy intake in patients with CKD, and this have not been systematically analyzed. We conducted this meta-analysis to identify and evaluate the effects of soy protein intake in patients with CKD.

Methods: A comprehensive search of Medline, Embase and the Cochrane Database of Systematic Reviews was performed in December 2013 and updated in April 2014 for any new trials. Randomized trials designed to evaluate the effects of dietary soy in patients with CKD were collected. Weighted mean effect sizes were calculated for net changes using random-effect or fixed-effect model. All statistical analysis were calculated by RevMan software 5.2 available free from the Cochrane Collaboration.

Results: 12 studies (280 participants) were included. And we found that dietary soy was associated with significant decrease of serum creatinine, serum phosphorus, CRP (C reactive protein)and proteinuria in the predialysis subgroup. The mean difference was −0.05 mg/dL (95% CI: −0.10, −0.00 mg/dL; $P = 0.04$) for serum creatinine, −0.13 mg/dL (95% CI: −0.26, −0.01 mg/dL; $P = 0.04$) for serum phosphorus, −0.98 mg/L (95% CI: −1.25, −0.71 mg/L; $P < 0.00001$) for CRP, and −0.13 mg/d (95% CI: −0.18, −0.08 mg/d; $P < 0.00001$) for proteinuria. We did not find any significant change in serum phosphorus, CRP in the dialysis subgroup. Blood urea nitrogen (BUN) was reduced with statistical significance in the soy-treated group compared with control when the predialysis and dialysis subgroup were analyzed as a whole. The pooled estimated effects of change for BUN was −0.37 mg/dL (95% CI: −6.03, −0.11 mg/dL; $P = 0.04$). No significant change was detected in creatinine clearance, glomerular filtration rate, serum albumin, body weight and body mass index(BMI).

Conclusions: Soy protein containing isoflavones intake significantly decreased serum creatinine, serum phosphorus, CRP and proteinura in predialysis patients, while no significant change was found in creatinine clearance and glomerular filtration rate. We also found that soy protein intake could maintain the nutritional status in dialysis patients, though no significant change in CRP, BUN, and serum phosphorus was detected. Future large, long-term RCTs are still needed to clarify the effects of soy protein intake in patients with CKD.

1. Introduction

Chronic kidney disease (CKD) has become an important problem affecting human health, and it is associated with increased risk of morbidity, mortality as well as huge healthcare costs [1]. Epidemiological studies indicate that CKD is also an independent risk factor for cardiovascular events, and the renin–angiotensin system (RAS), oxidative stress, inflammation and hemodynamic disorders are reported to be involved in this pathophysiological process [2].

Previous studies have demonstrated the beneficial effects of dietary soy in humans and animal models. Frigolet et al. [3]. concluded that, soy protein is capable of attenuating abnormal expression of renin–angiotensin. An in vitro and in vivo study conducted by Jia et al. [4]. found that, genistein, a soy isoflavones, protects against inflammation induced by TNF-α in vascular endothelial cells. And oxidative stress was significantly decreased in postmenopausal women when treated with soy isoflavones [5].

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Moreover, a recent population-based study suggested soy or soy isoflavones intake significantly reduced the risk of postmenopausal breast cancer [6]. These beneficial findings have been applied for the development of preventive strategies for human health and disease. For example, the US Food and Drug Administration suggested that "25 g soy protein per day" may help prevent the risk of coronary heart disease because of reduced serum lipids and lipoproteins [7].

Emerging evidence from animal and human studies demonstrated that dietary soy protein containing isoflavones retard the development and progression of renal dysfunction. Reportedly, dialysis patients in japan where mean soy products consumption is significantly higher than that in the United State tend to live longer than patients in the US [8,9]. Iwasaki et al. [10] found Fisher rats in the soy diet group tend to have longer life than that in the casein-treated group, and the progression of renal dysfunction was obviously delayed when casein protein was replaced with soy protein. As a result, following the publication of several randomized, clinical trials, our attention has been directed to manipulate the dietary protein quality especially by replacing animal protein with soy protein that rich in isoflavones. Ogborn et al. [11] found that soy protein significantly ameliorate aging-related nephropathy in Fisher 344 rat and renal dysfunction in 5/6 nephrectomy mouse models. Furthermore, observational studies in patients with diabetic nephropathy demonstrated substitution of soy protein for animal protein results in decreased glomerular hyperfiltration and less proteinuria, whereas Marion et al. have not achieved the aim of attenuating proteinuria in the soy-treated group compared with control [12,13].

As described above, studies evaluating the effects of dietary soy in the management of CKD have demonstrated mixed findings, and these results were few systematically reviewed. As a result, this meta-analysis was designed to explore the effects of soy protein containing isoflavones intake in patients with CKD.

2. Methods

2.1. Search strategy

A systematic literature search was performed in Medline, Embase and the Cochrane Database of Systematic Reviews for clinical trials evaluating the effects of soy diets, soy protein, or soy isoflavones in patients with CKD in December 2013 and updated in April 2014 for any new trials. The search strategies used were as follows, [(soy OR soybean OR soya OR soy protein OR isoflavones OR isoflavone OR genistein OR daidzein)] AND [(chronic kidney disease OR kidney failure OR chronic kidney failure OR kidney disease OR uremia OR dialysis OR continuous ambulatory peritoneal dialysis OR hemodialysis OR renal replacement therapy OR peritoneal dialysis OR Equilibrium dialysis OR extended daily dialysis)]. Only randomized controlled trials (RCTs) were identified for inclusion without any language limitation in our study. Title and abstract of each article was screened carefully for inclusion at the first step of retrieval process. Then all potentially relevant articles were examined carefully in full text for further identification. Reviews and meta-analyses on effects of soy diets or soy protein in patients with CKD were also checked seriously for any potential trials. Meanwhile, the cited references of each included studies were scanned carefully for additional trials or reviews. Trials were analyzed as a whole once it had more than one publication.

2.2. Selection criteria

Randomized, controlled trials with a crossover or parallel design that were of at least 7 weeks follow-up and designed to evaluate the effects of soy diets, soy protein or soy isoflavones in patients with CKD (including the dialysis patients) were identified. Only adult patients (over 18 years old) with renal dysfunction or kidney failure were eligible for inclusion. As for the initial screening process, the main exclusion criteria were as follows: participants younger than 18 years old; other outcomes such as bone metabolism, serum lipid levels; pharmacokinetics and basic studies; trials treated with isoflavones-depleted soy protein or isoflavones that is not extracted from soybeans; patients with renal transplantation; reviews and editorials.

2.3. Data extraction and quality assessment

Data were collected independently from each included RCT, and any discrepancies were figured out by consensus. For those included trials, data were extracted based on a standardized strategies, including publications, study designs, size of study population, type of diet, characteristics of participants (such as age, gender, and treatment modality, etc.), interventions, the contents of isolated soy protein (ISP) and isoflavones, the main outcomes (such as serum creatinine, 24-h urine protein excretion, blood urea nitrogen, etc.), and duration of follow-up. As for Imani et al. [14]. that did not provide the contents of isoflavones, we calculated it based on the concentration of isoflavones in traditional soy products which is about 3.5 mg isoflavones per 1 g soy protein [15].

Methodological quality and risk of bias of each included RCT were examined carefully using the method described by the Cochrane Collaboration [16]. The items were as follows, 1. Random sequence generation; 2. Allocation concealment; 3. Blinding of participants and personnel; 4. Blinding of outcome assessment; 5. Incomplete outcome data; 6. Selective reporting; 7. Other sources of bias. All seven items were classified as "low risk of bias", "high risk of bias", or "unclear risk of bias". Furthermore, intention-to-treat analysis (ITT) was also used to evaluate integrity of the outcome data.

2.4. Statistical analyses

We grouped studies based on the mode of treatment as described above into the non-dialysis group and the dialysis group. Results were also calculated separately for subgroup analysis. Data from each included trials were analyzed using Review Manager (RevMan, Version 5.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Treatment effects were presented as the mean differences between changes and its 95% confidence intervals (CI), and the pooled effects were computed by assigning each trial a weight of the reciprocal of its variance. And if the raw data were unavailable, the variances for the changes of individual trials were calculated according to the methods described by the Cochrane Collaboration. Heterogeneity of treatment effects was evaluated using the x^2 test, and the I^2 test for inconsistency. The degree of inconsistency among those identified trials was defined by calculating the percentage of total between-study variation because of heterogeneity rather than random variation as the I^2 metric using the formula $I^2 = 100\% \times (\text{Q-df})/Q$ [17]. We described the results using random-effect model when heterogeneity across those trials was significant, and on the contrary, a fixed-effect model was applied [18].

Though the outcomes evaluated in this meta-analysis have limited number of trials, the funnel plots calculated using the Review Manager 5.2 were used to assess the presence or absence of publication bias for certain outcomes. The P-value threshold for statistical significance was set at 0.05 for effect size, $P \leq 0.05$ was considered significant.

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