Systematic review and meta-analysis of the effects of high protein oral nutritional supplements

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CRD summary
The review concluded that high protein oral nutritional supplements had significant clinical, nutritional and functional benefits in a range of patient groups and health settings. The authors' conclusions are reasonable but considerable clinical diversity in the included studies causes some uncertainty as to their generalisability.

Authors' objectives
To evaluate the efficacy of high protein oral nutritional supplements for adults of any nutritional status.

Searching
PubMed, The Cochrane Library, Clinical Evidence, NeLH, Trip, CINAHL and National Service Frameworks were searched to 4 January 2010 for studies published in English; search terms were reported. Bibliographies of relevant studies were checked and experts were contacted. Only full papers were considered.

Study selection
Randomised controlled trials (RCTs) of high protein oral nutritional supplements were eligible for inclusion. Studies were of adults (≥18 years) of any nutritional status in any setting. There were no restrictions on comparator type. High protein ONS could be of any consistency, should contain two or more macronutrients and contain at least 20% of its energy provided by protein. The intervention could be of any duration, provide some or the entire daily energy requirement and be nutritionally complete or incomplete. Studies of pregnancy and lactation, parenteral nutrition, enteral tube feeding, sports studies and in developing countries were excluded. Relevant outcomes included clinical and healthcare use and functional and nutritional outcomes.

Studies were mostly in community settings. Energy density of the supplement ranged from 0.75 to 3.85kcal/mL, with a prescribed daily energy intake of 149kcal to 995kcal and daily protein intake of 10g to 60g. Interventions ranged from two weeks to two years (mean three months). Comparators were placebo, standard diets and dietary counselling. Most participants were elderly (mean age 42 to 86 years).

One reviewer performed the study selection, which was checked by a second reviewer.

Assessment of study quality
Methodological study quality was assessed using the five-point Jadad scale of randomisation, blinding and withdrawals to give scores up to 5.

One reviewer made the assessment and this was checked by a second. Any discrepancies were resolved by discussion.

Data extraction
Data were extracted to enable calculation of odds ratios (ORs) or mean differences (MDs), with associated 95% confidence intervals.

The authors did not report how many reviewers performed the data extraction.

Methods of synthesis
Results were pooled for trials that reported the same outcomes in the same way. Studies were predominately pooled using a random-effects model to give odds ratios or mean differences each with 95% CIs. Between-study heterogeneity was assessed using the $I^2$ statistic and reported for the fixed-effect meta-analyses. Studies that compared high protein supplements with standard supplements were analysed separately from studies that used other types of controls. Subgroup analyses were performed according to study setting. Meta-regressions were performed to investigate the impact of potential confounding factors.
Results of the review
Thirty-six RCTs were identified (3,790 participants, range 10 to 672). Follow-up ranged from 10 days to two years. Jadad scores ranged from 1 or 2 (18 studies) to 4 or 5 (10 studies).

Clinical and healthcare use: High protein supplements had a significant benefit versus controls for reducing complications (OR 0.68, 95% CI 0.55 to 0.83; 10 RCTs), nausea/vomiting (OR 0.74, 95% CI 0.60 to 0.90; 13 RCTs), length of stay (MD -3.77 days, 95% CI -7.37 to -0.17; nine RCTs) and readmissions (OR 0.59, 95% CI 0.41 to 0.84; two RCTs; I²=0.0%; fixed-effect model). There was no significant difference in mortality for high protein supplements versus controls (15 studies).

Functional outcomes: High protein supplements had a significant benefit versus controls for grip strength (MD 1.76kg, 95% CI 0.36 to 3.17; four RCTs). There was no evidence of a statistically significant benefit with high protein supplements compared to controls for activities of daily living or mobility and results were mixed for breathlessness. Most studies of quality of life showed a statistically significant benefit with high protein supplements compared to controls.

Nutritional outcomes: High protein supplements versus controls significantly increased total energy intake (MD 314kcal, 95% CI 146 to 482; 12 RCTs) and total protein intake (MD 22g, 95% CI 10 to 34; 10 RCTs). High protein supplements significantly increased weight gain compared to controls (MD 1.7kg, 95% CI 0.8 to 2.7; 12 RCTs). The effect on oral food intake and appetite was unclear.

High protein versus standard supplements (three RCTs): No significant differences for most outcomes but one study found a significant improvement for weight gain, body mass index and fat mass.

Authors’ conclusions
There were clinical, nutritional and functional benefits resulting from high protein oral nutritional supplement use in a range of patient groups and health settings. The available evidence suggested little suppression of normal food intake, with the high protein supplement being mostly additive to food intake. There was inadequate information to compare standard and high protein supplements.

CRD commentary
The review addressed a well-defined question in terms of study design, participants and interventions; outcomes were less clearly defined. Relevant databases were searched for published and unpublished trials. Only studies fully published in English were included so some relevant studies may have been missed. Publication bias was not assessed. Study quality was assessed using suitable criteria and varied widely. Efforts were made to reduce error and bias in study selection and quality assessment but it was not reported whether similar efforts were made for data extraction. Relevant study details were reported.

The synthesis was appropriate. It was difficult to assess the extent of statistical heterogeneity from the data reported but it was apparent from the study characteristics that the populations and interventions were highly diverse. This was partly addressed by investigating the impact of several study characteristics on the results but this was constrained by the number of studies available.

Two authors were employed by Nutricia, Advanced Medical Nutrition.

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Implications of the review for practice and research
Practice: The authors recommended that when providing oral nutritional supplements in clinical practice, patients’ nutritional status and requirements should be considered, goals set and treatment monitored.

Research: The authors suggested that future studies should include more patients (particularly when comparing high protein and standard supplements. Studies should take into account whether the patient had a low protein intake and was suffering from catabolic effects of disease or increased protein losses and whether an additional supply of amino acids might facilitate wound repair and other essential tissue functions. Future research should also address the type of

protein used in the supplement (such as casein, whey, soy protein).

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