

## Nutritional and health benefits of semi-elemental diets: A comprehensive summary of the literature

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### Abstract

**AIM:** To critically review and summarize the literature on nutritional and health outcomes of semi-elemental formulations on various nutritionally vulnerable patient populations who are unable to achieve adequate nutrition from standard oral diets.

**METHODS:** We conducted a comprehensive literature search of Pubmed and Embase databases. We manually screened articles that examined nutritional and health outcomes (*e.g.*, growth, disease activity, gastrointestinal impairment, mortality, and economic impact) among various patient groups receiving semi-elemental diets. This review focused on full-text articles of randomized controlled clinical trials and other intervention studies, but pertinent abstracts and case studies were also included. Results pertaining primarily to tolerance, digestion, and absorption were summarized for each patient population in this systematic review.

**RESULTS:** Results pertaining primarily to tolerance, digestion, and absorption were summarized for each patient population. The efficacy of semi-elemental whey hydrolyzed protein (WHP) diet have been reported in various nutritionally high risk patient populations including - Crohn's disease, short bowel syndrome, acute and chronic pancreatitis, cerebral palsy, cystic fibrosis, cerebrovascular accidents, human immunodeficiency virus, critically ill, and geriatrics. Collectively, the evidence from the medical literature indicates that feeding with a semi-elemental diet performs as well or better than parenteral or amino acid based diets in terms of toler-

ance, digestion, and nutrient assimilation measures across various disease conditions.

**CONCLUSION:** Based on this comprehensive review of the literature, patient populations who have difficulty digesting or absorbing standard diets may be able to achieve improved health and nutritional outcomes through the use of semi-elemental WHP diets.

**Key words:** Semi-elemental diet; Malnutrition; 100% hydrolyzed whey protein; Nutrition; Malabsorption

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**Core tip:** Patients with major chronic illnesses may not be able to achieve adequate macronutrient or micronutrient requirements through standard oral diet because of difficulties tolerating, digesting, or absorbing whole foods. In our systematic review, we summarized the literature on the numerous nutritional and health benefits of semi-elemental formulations across various nutritionally vulnerable patient populations. Overall, the literature demonstrates that semi-elemental diet performs consistently as well or better than parenteral or amino acid based diets in terms of tolerance, digestion, and nutrient assimilation measures across various disease conditions.

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## INTRODUCTION

Nutrition plays a significant role in achieving optimal health, but in certain high risk populations with significant systemic illnesses, achieving adequate nutrition with a traditional oral diet maybe difficult secondary to inability to tolerate, digest, and absorb whole foods. In these nutritionally-vulnerable populations, additional nutritional support *via* parenteral nutrition (PN) or enteral nutrition (EN) is necessary. When feasible, EN is clearly favored over PN because of fewer infectious complications, reduced healthcare costs, improved return of gut function, and reduced length of hospital stay<sup>[1]</sup>.

Elemental diet formulas are used to provide liquid nutrients in a form that is easily and readily assimilated. Such diets provide protein in the form of individual amino acids and may provide a portion of the fat calories as medium chain triglycerides (MCT). These diets are typically reserved for individuals transitioning off of PN or with severe gastrointestinal pathology that prevents normal digestion, absorption or motility.

Semi-elemental formulas, however, contain peptides of varying chain length, and fat primarily as MCT<sup>[2,3]</sup>. While semi-elemental diets are slightly more expensive than polymeric diets (formulas containing intact protein, complex carbohydrates, and long chain triglycerides), they are widely used because it is suggested that they are better absorbed and tolerated in patients with malabsorptive conditions and are more palatable than conventional elemental formulations<sup>[2]</sup>.

A large volume of clinical studies have demonstrated significant health benefits with semi-elemental diets in all phases of the dietary process<sup>[4-6]</sup>. Indeed, such diet formulas have been shown to reduce the degree of regurgitation, gastric emptying times, and gagging while improving tolerance<sup>[7,8]</sup>. As a result, studies have suggested improved growth and development patterns, fewer gastrointestinal complications, improved visceral protein levels, and decreased rates of mortality. Studies of patients with Crohn's disease, pancreatitis, and human immunodeficiency virus (HIV) among other conditions have shown improved nutrition status and clinical outcomes from supplemental semi-elemental formulas<sup>[9-12]</sup>. The purpose of this review is to comprehensively summarize the scientific and clinical evidence of 100% whey-hydrolyzed protein (WHP) semi-elemental diets and nutritional and health outcomes across various nutritionally-vulnerable populations.

## MATERIALS AND METHODS

We conducted a comprehensive literature search using the MEDLINE biomedical literature database, accessed from PubMed and the Embase database. The literature search and study identification process utilized in this review was different and more complex than typical literature reviews. This is a broad and dynamic topic area that covers many formula comparisons (*e.g.*, semi-elemental WHP diets vs amino acid based diets), nutritional and health outcomes (*e.g.*, growth, disease activity, gastrointestinal impairment, mortality, economic impact), and patient populations (*e.g.*, Crohn's disease, pancreatitis, stroke, critically ill patients). Given this diversity, we incorporated an all-inclusive approach to study designs such that we included all lines of human health evidence. Specifically, we focused on results from randomized controlled clinical trials and prospective intervention studies. In addition, results from relevant observational studies, case reports and series, and abstracts were included.

Relevant studies were identified through a comprehensive series of individual literature searches using a wide variety of keywords and search terms, such as - but not limited to - "semi-elemental diet", "semi-elemental formula", "peptide based diet", and "enteral nutrition". The literature search was limited to English-language publications with no prior date truncations. We supplemented our literature search by manually reviewing the reference lists of relevant articles to

identify any additional studies. Studies that combined treatment of semi-elemental WHP diets with other treatments, such as corticosteroids, or included patient populations less than one year of age were excluded from this review. Given the between study variation across the literature, we did not attempt to combine data quantitatively in a meta-analysis format.

## RESULTS

### **Crohn's disease**

Studies of 100% WHP and Crohn's disease are characterized in Table 1<sup>[5,10,11,13-25]</sup>. In a one year prospective study, six Crohn's disease patients (median age, 13.6 years) were treated with an isotonic, 100% WHP semi-elemental diet to evaluate growth parameters and disease activity measures<sup>[11]</sup>. Significant increases in height and weight velocity as well as significant improvement in clinical disease activity as measured by the Crohn's disease activity index, albumin, somatomedin C, and improvement in growth failure were observed in all patients. Similarly, in an open-label pilot study at two pediatric centers, Hussey *et al.*<sup>[13]</sup> observed excellent tolerance and efficacy of a six-week tube feeding regimen of a 100% WHP semi-elemental diet among active Crohn's disease patients (mean age 11.4 ± 2.3 years). Throughout the study, the formula was well-tolerated, and subjects demonstrated significant gains in weight, height and achieved improved nutritional status. In addition, inflammation and disease activity was decreased with a resulting improved quality of life as measured by pediatric inflammatory bowel disease questionnaire<sup>[13]</sup>.

Royall *et al.*<sup>[14]</sup> conducted a randomized controlled trial among patients with active Crohn's disease to evaluate clinical and nutritional outcomes comparing a peptide-based 100% WHP diet with an amino acid-based elemental diet. After three weeks, clinical remission rates were similar in the amino acid group compared with the peptide group. The authors concluded that peptide-based diets are equally efficacious as amino acid-based diets in terms of high rates of clinical remission and is better tolerated orally<sup>[14]</sup>. In another randomized controlled study, Mansfield *et al.*<sup>[15]</sup> compared the efficacy of a 100% WHP diet with an amino acid-based diet to achieve remission in 44 patients with active Crohn's disease. After four weeks of treatment, exactly similar clinical remission rates of 36% were achieved in both the 100% WHP diet group and the elemental diet group, but the 100% WHP diet was much better tolerated orally<sup>[15]</sup>.

In another trial, 22 patients suffering from moderately active Crohn's disease were randomized to receive treatment with a 100% WHP semi-elemental diet as monotherapy ( $n = 10$ ) or corticosteroids ( $n = 10$ )<sup>[17]</sup>. After two weeks of treatment, there were significant improvements in the Crohn's disease activity index, body mass index, and prealbumin level among patients

treated with the 100% WHP diet and the results were statistically similar to corticosteroids across all measured parameters. However, the 100% WHP diet was well-tolerated with less side effects. Collectively, these studies demonstrate that in patients with moderate to severely active Crohn's disease, semi-elemental formula may be a viable alternative to corticosteroids at inducing clinical remission, improving lean body mass, reducing risk for growth failure, and enhancing the probability of maintaining clinical remission.

### **Short bowel syndrome and intestinal failure**

Several studies have evaluated the role of semi-elemental feedings as primary nutritional therapy among patients who have undergone extensive gastrointestinal resection. In an initial case report, Rodriguez *et al.*<sup>[26]</sup> reported a 62-year-old male who underwent extensive bowel resection with resulting short bowel syndrome. He was treated with a 100% WHP semi-elemental tube feeding regimen for 112 d and demonstrated an improved nutritional state with improvement in visceral protein levels without need for parenteral nutrition. In a retrospective study of 85 pediatric patients with short bowel syndrome who underwent an intestinal transplantation (median age at transplant, 2.7 years), patients on semi-elemental product reached full feeds faster than patients who were started on an amino acid formula (3 mo vs 5 mo) because of better oral tolerance. In a crossover study among six children with short bowel syndrome, patients were treated with a semi-elemental diet followed by a free amino acid (FAA) diet<sup>[24]</sup>. The results showed that while fat excretion was identical in both formulas and stool electrolyte excretion was not significantly different, trace element analysis demonstrated that copper ( $P = 0.0002$ ) and sulfur ( $P = 0.02$ ) excretion was much greater for the FAA diet, suggesting a benefit from semi-elemental formulation with regards to micronutrient absorption. The authors concluded that treatment with peptide-based enteral formula after an intestinal transplant may provide more nutritional benefits among pediatric patients compared to patients who receive an amino-based formula, likely through more efficient micronutrient and nitrogen absorption.

### **Pancreatitis**

Studies of 100% WHP and pancreatitis are characterized in Table 2<sup>[6,9,27-32]</sup>. In a prospective pilot study conducted by Tiengou *et al.*<sup>[27]</sup>, patients with severe acute pancreatitis who required nasojejunal nutrition were randomized to receive a 100% WHP semi-elemental diet ( $n = 15$ ) or a standard polymeric formula ( $n = 15$ ) for seven days. Both formulas were well tolerated in patients with acute pancreatitis, though the group on semi-elemental 100% WHP formula provided a more favorable clinical course because it was associated with less weight loss ( $P = 0.001$ ), a significantly shorter hospital duration ( $P = 0.006$ ), and a trend towards

Table 1 Selected studies of semi-elemental whey hydrolyzed protein diets and Crohn's disease and other gastrointestinal complications

Ref.	Study population	Design	Feeding mode (comparison)	No. patients (comparison)	Feeding duration	Relevant results <sup>1</sup>
Polk <i>et al</i> <sup>[11]</sup>	Children, tanner stage I-II, mean age 13.6	Prospective cross-over	Isotonic hydrolyzed whey formula administered <i>via</i> nocturnal nasogastric infusion (patients served as their controls based on observations at least a year before the study)	6 (6, served as own controls)	Intermittent diet program for 1 yr	Height increased $2.6 \pm 0.8$ to $9.3 \pm 0.9$ cm/yr ( $P < 0.0001$ ) Weight increased $3.0 \pm 1.2$ to $6.63 \pm 1.2$ kg/yr ( $P < 0.02$ ) Somatomedin C increase $0.7 \pm 0.1$ to $1.8 \pm 0.3$ UL ( $P < 0.0001$ ) Albumin increase $3.4 \pm 0.2$ to $4.0 \pm 0.1$ g/dL ( $P < 0.0003$ ) CDAI increase $64 \pm 3.4$ to $80.1 \pm 2.2$ ( $P < 0.01$ ) (disease activity inversely correlates with numerical score)
Hussey <i>et al</i> <sup>[13]</sup>	Children with active CD, mean age 11.4	Prospective, NR, open-label pilot	Peptamen with Prebio <i>via</i> nasogastric tubes	10 - single group	6 wk	Height increased $143.8 \pm 13$ to $144.5 \pm 13.1$ cm ( $P < 0.01$ ) Weight increases $31.9 \pm 7.2$ to $36.5 \pm 8.1$ kg ( $P < 0.0001$ ) PCDAI decrease $40 \pm 13$ to $5 \pm 6$ ( $P < 0.0001$ ) (lower score corresponds to lower disease activity) Albumin increase $3.1 \pm 0.4$ to $3.8 \pm 0.4$ g/dL ( $P < 0.01$ ) PEDIBDQ increase $198 \pm 31$ to $243 \pm 34$ ( $P < 0.01$ ) (higher score indicating better quality of life)
Royall <i>et al</i> <sup>[14]</sup>	Adults with moderate to severely active CD	RCT	Peptamen administered <i>via</i> a nasoduodenal feeding tube (Vivonex-TEN, amino acid based formula)	21 (19)	3 wk	Remission rates after 3 wk: 75% in the peptide group, 84% in the amino acid group Remission rates after 1 yr: 40% in the peptide group, 31% in the amino acid group Weight increased $2.0 \pm 0.5$ kg in the peptide group and $1.7 \pm 0.3$ kg in the amino acid group ( $P < 0.0005$ within group differences after 3 wk) Total phospholipids (mg/mL) concentration increase in the peptide group ( $1.37 \pm 0.1$ to $1.71 \pm 0.15$ ) ( $P < 0.025$ ) (no difference in amino acid group)
Mansfield <i>et al</i> <sup>[15]</sup>	Adults with active CD	RCT	Pepti-2000 LF Liquid received through nasogastric tube (Elemental 028)	22 (22)	4 wk	Remission rates after 4 wk: 36% in the Pepti-2000 group and 36% in the E028 group Mean percent ideal body weight: Pepti-2000 group increased from $92 \pm 4$ to $95 \pm 4$ and E028 group remained the same at $83 \pm 5$
Middleton <i>et al</i> <sup>[16]</sup>	Adults with active CD	RCT	Pepdite 2+ given orally or through nasogastric tube if necessary (Elemental 028/Elemental 028 + LCT/Elemental 028 + MCT)	18 (17/22/19)	3 wk	Remission rates after 3 wk: 87% in Pepdite 2+ group, 92% in the E028 group, 55% in the E028 LCT group, and 92% in the E028 MCT group Mean CRP: Decreased significantly in E028 group and E028 MCT group, but non-significantly decreased in Pepdite 2+ group and E028 LCT group (values not provided)
Zoli <i>et al</i> <sup>[17]</sup>	Adults with moderately active CD	RCT	Peptamen received orally (0.5 mg/kg per day prednisolone)	10 (10)	2 wk	Peptide group: CD activity score (CDAS): $5.6 \pm 0.8$ to $2 \pm 1.4$ ( $P < 0.01$ ) ESR: $21.4 \pm 6$ to $16.7 \pm 6.7$ ( $P < 0.05$ ) Permeability index: $4.9 \pm 5.3$ to $2.1 \pm 2$ ( $P < 0.01$ ) BMI: $18.5 \pm 3$ to $19.2 \pm 3.1$ ( $P < 0.02$ ) Prealbumin: $22.2 \pm 8$ to $23.5 \pm 7.8$ ( $P < 0.01$ ) Retinol binding protein: $3.7 \pm 0.7$ to $4 \pm 0.8$ ( $P < 0.02$ ) <i>In vivo</i> cell-mediated immunity (Multitest IMC): $4.2 \pm 2.1$ to $5.9 \pm 2.3$ ( $P < 0.01$ ) (in the corticosteroid group, there were significant findings for improvement of simple CD activity index and fat free mass)

Pereira <i>et al</i> <sup>[18]</sup>	Adults with mildly active CD and healthy laboratory staff	Follow-up study (secondary study)	Peptamen received orally (0.5 mg/kg per day prednisolone)	13 CD patients (17 healthy controls)	2 wk	No significant differences between groups in clinical response to treatment, markers of disease activity, or plasma phospholipid classes (data not reported)
Malchow <i>et al</i> <sup>[19]</sup>	Adults with active CD	RCT	Survimed given orally (12-48 mg/d 6-methyl prednisolone and 3 g/d sulfasalazine)	51 (44)	6 wk	Percent underweight after 3 wk: 15.1% in Survimed group and 13.4% in steroid group Crohn's disease activity index after 3 wk: 87.2 in Survimed group and 88.8 in steroid group Number of soft stools per week after 3 wk: 43.2 in Survimed group and 60.0 in steroid group Remission rates after 6 wk: 52.7% in the Peptisorb group and 78.8% in the steroid group ( $P < 0.01$ ) Body weight: increased in Peptisorb group from 55.6 ± 1.8 kg to 58.9 ± 1.6 kg, and increased in steroid group from 53.5 ± 1.3 kg to 56.8 ± 1.2 kg after treatment Number of soft stools per week: Decreased in Peptisorb group from 31.9 ± 4.3 to 9.7 ± 1.8 and decreased in steroid group from 37.1 ± 2.9 to 9.4 ± 1.5 after treatment
Lochs <i>et al</i> <sup>[20]</sup>	Adults with acute active CD	RCT	Peptisorb received through nasogastric tube (12-48 mg/d 6-methyl prednisolone and 3 g/d sulfasalazine)	55 (52)	6 wk	Decrease in Crohn's disease activity index of 50 points or more after 1 mo: 33% in vital HN group and 70% in steroid group
Lindor <i>et al</i> <sup>[21]</sup>	Adults with active CD	RCT	Vital HN received orally or through nasogastric tube if necessary (0.75 mg/kg per day prednisone)	9 (10)	1 mo	Remission rates after 6 wk: 72% (47%-90%) in Twinline group and 67% (41%-87%) in the Elental group Crohn's disease activity index after 6 wk: 82 in Twinline group and 102 in Elental group Flatulence/gas among 9 children with a neurological disorder: Significantly less for the fiber formula ( $P < 0.05$ ) Frequency of bowel movements: No difference between groups ( $P > 0.05$ ) Stool frequency in the CD group: Higher with the fiber formula but no change in consistency (data not reported)
Sakurai <i>et al</i> <sup>[22]</sup>	Adults with active CD	RCT	Twinline received through nasogastric tube (Elental)	18 (18)	6 wk	Weight change: Mean loss of 5.1% in the semi-elemental/polymeric group, mean gain of 5.7% in the isocaloric, isotonic, semi-elemental formula with prebiotics group
Khoshoo <i>et al</i> <sup>[5]</sup>	Children with gastrointestinal dysmotility ( $n = 9$ ), CD ( $n = 3$ ), mild short bowel syndrome ( $n = 2$ )	Randomized, double-blind, cross-over clinical study	Peptamen Junior and Peptamen Junior with fiber and prebiotics	14	1 formula for 2 wk, 5 d washout, 2 <sup>nd</sup> formula for 2 wk	
Parekh <i>et al</i> <sup>[23]</sup>	Patients undergoing intestinal rehab with varying diseases [radiation enteritis ( $n = 5$ ), ulcerative colitis ( $n = 1$ ), bowel volvulus ( $n = 1$ ), mesenteric ischemia ( $n = 1$ )]	Cross-over study	Semi-elemental/polymeric diet with a switch to an isocaloric, isotonic, semi-elemental formula with prebiotics	2 (6)	4.9 mo after an initiation of 60 d post-abdominal resection; second diet for a mean of 2.9 mo	
Hamaoui <i>et al</i> <sup>[10]</sup>	Patients undergoing major abdominal surgery	Randomized prospective study	Reabilan HN, small peptide based formula <i>via</i> jejunostomy (equicaloric isonitrogenous total PN)	11 (8)	Primary analyses within 1 wk of enrollment	Mean daily stool output: 93.1 ± 68.5 g/d in the Reabilan group, 22.2 ± 35.3 g/d in the PN group ( $P < 0.05$ ) No significant differences between groups for serum albumin, prealbumin, or plasma transferrin Average daily cost of supplies: \$44.36 ± 8.50 for the Reabilan group, \$102.10 ± 11.77 for the PN group ( $P < 0.001$ ); non-nutrient supplies accounted for 13% of the cost in the Reabilan group vs 43% in the PN group
Kowalski <i>et al</i> <sup>[25]</sup>	Patients who received a post IIX	Retrospective case review	Peptide product (amino acid product)	34 (15)	Primary analyses within 6 mo	Time to full feedings post IIX from baseline to 1 to 2 yr: Peptide group z-scores: -2.71, -2.36, -2.32 (monotonic trend) Amino acid group z-scores: -2.46, -2.29, -2.35 Time to reaching full feeds (among those receiving rATG therapy): 3 mo in the peptide group, 5 mo in the amino acid group ( $P > 0.05$ )

Murray <i>et al</i> <sup>[24]</sup>	Children with short bowel syndrome	Randomized cross-over study	Peptamen (Vivonex TEN, high carbohydrate)	6	Two, 7 d periods	Mean ostomy output: 39 cc/kg per day in the Peptamen group, 49 cc/kg per day in the Vivonex TEN group Fat excretion: Identical in both groups ( $P = 0.9$ ) Trace element analysis: Greater excretion of copper ( $P = 0.0002$ ) and sulfur ( $P = 0.02$ ) in the Vivonex TEN group
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<sup>1</sup>Numerous results are reported within individual studies, please refer to the studies for a full summary of results. RCT: Randomized controlled clinical trial; NR: Non-randomized; CD: Crohn's disease; CDAI: CD activity index; PCDAI: Pediatric CD activity index; PEDIBDQ: Pediatric inflammatory bowel disease questionnaire; LCT: Long-chain triglycerides; MCT: Medium-chain triglycerides; ESR: Erythrocyte sedimentation rate; BMI: Body mass index; PN: Parenteral nutrition; ITx: Intestinal transplant.

**Table 2 Selected studies of semi-elemental whey hydrolyzed protein diets and pancreatitis**

Ref.	Study population	Design	Feeding mode (comparison)	No. patients (comparison)	Feeding duration	Relevant results <sup>1</sup>
Tiengou <i>et al</i> <sup>[27]</sup>	Consecutive patients with acute pancreatitis admitted to a gastroenterology and nutrition department	Randomized prospective pilot study	Peptamen (polymeric diet group, sondalis-Iso)	15 (15)	1 wk	Weight (kg): $-1.3 \pm 1.1$ in the peptide group, $-2.4 \pm 0$ in the polymeric group ( $P < 0.01$ ) Total hospital stay (d): $23 \pm 2$ in the peptide group, $27 \pm 1$ in the polymeric group ( $P = 0.006$ ) Infection: 1/15 in the peptide group, 3/15 in the polymeric group (NS) C-reactive protein: Reduced 50% at a median of 5 d faster for the peptide group (6 d) vs the PN group (11 d) ( $P = 0.09$ ) Serum cholecystokinin: 56 pmol/L to 55 pmol/L ( $P = 0.2$ ) in the peptide group, 42 pmol/L to 32 pmol/L in the PN group ( $P = 0.5$ ) Mortality: 0 deaths in the peptide group, 3 deaths in the PN group (attributable to complications of pancreatitis) Economic cost: Peptide group = \$1375, PN group = \$2608 ( $P = 0.08$ ); when 1 NJ tube used: Peptide group = \$1086, PN group = \$2608 ( $P = 0.03$ )
Louie <i>et al</i> <sup>[9]</sup>	Consecutive patients with acute pancreatitis in an academic, multi-institutional, tertiary care system	RCT	Peptamen administered <i>via</i> nasojejunal feeding tubes (parenteral nutrition, intralipid administered <i>via</i> long-term vascular catheters)	10 (18)	Primary analyses within 1 wk of enrollment	Length of ICU stay (d): $1.3 \pm 0.9$ in the peptide group, $2.8 \pm 1.3$ in the PN group (NS) Length of hospital stay (d): $9.7 \pm 1.3$ in the peptide group, $11.9 \pm 2.6$ in the PN group (NS) Economic cost: \$761 $\pm$ 50.3 in the peptide group, \$3294 $\pm$ 551.9 in the PN group ( $P < 0.005$ )
McClave <i>et al</i> <sup>[28]</sup>	Patients with acute pancreatitis or an acute flare of chronic pancreatitis	RCT	Peptamen infused through a nasojejunal tube (total parenteral nutrition infused through a central or peripheral line)	16 (16) (30 patients over 32 admissions)	Primary analyses within 1 wk of enrollment	Septic complications: 27.8% in peptide group, 50% in PN group ( $P < 0.01$ ) Any complications: 44.4% in peptide group, 75% in PN group ( $P < 0.05$ ) Mean stay in ICU: 11 d in peptide group, 12 d in PN group (significance not provided)
Kalfarentzos <i>et al</i> <sup>[32]</sup>	Patients with acute pancreatitis admitted to surgery unit	Randomized prospective trial	Reabilan HN administered <i>via</i> nasoenteric feeding tube (parenteral nutrition as all-in-one continuous subclavian polyurethane catheter infusion)	18 (20)	Mean: 34.8 d (mean: 32.8 d)	Necrosis: 29% in peptide group, 33% in PN group (NS) Septic complications: 12% in peptide group, 27% in PN group ( $P = 0.08$ ) Surgery: 12% in peptide group, 23% in PN group (NS) Severe pancreatitis: 17% in peptide group, 21% in PN group (NS) Death: 4.9% in peptide group, 8.3% in PN group (NS)
Oláh <i>et al</i> <sup>[29]</sup>	Patients admitted to surgical ward with a diagnosis of acute pancreatitis	Two-phase controlled prospective trial	Survimed administered <i>via</i> NJ tube (parenteral nutrition as an all-in-one venous admixture)	41 (48)	5-9 d (5-16 d)	

Petrov <i>et al</i> <sup>[30]</sup>	Patients with severe acute pancreatitis	RCT	Peptamen administered through NJ tube (parenteral nutrition administered through central venous catheter)	35 (34)	Assessment on day of feed commencement, fourth and seventh days	Pancreatic infection: 20% in peptide group, 47% in PN group ( $P = 0.022$ ) Noninfectious complications: 42.9% in peptide group, 17.6% in PN group ( $P = 0.036$ ) Serum CRP concentration: 195 (164-216) mg/L on admission to 94 (56-117) mg/L on day 7 in peptide group, 210 (177-246) mg/L on admission to 93 (60-134) on day 7 in PN group (NS) Mortality: 6% in peptide group, 35% in PN group ( $P = 0.003$ )
Kumar <i>et al</i> <sup>[41]</sup>	Consecutive patients with severe acute pancreatitis	Randomized pilot study	Peptamen administered through enteral tubes in both groups; patients were randomly allocated to NG or NJ feeding	15 NG, 16 NJ	1 wk	Hospital stay (d): 29.93 ± 25.54 in NJ group, 24.06 ± 14.35 in NG group ( $P = 0.437$ ) Mortality: 4/14 in NJ group, 5/16 in NG group Recurrence of pain: 1/14 in NJ group, 1/16 in NG group Serum albumin: No significant differences Anthropometric measurements: No significant differences in BMI, mid upper arm circumference, and triceps skin fold thickness) Healthy controls: Postprandial plasma CCK: Mean basal CCK levels = 0.46 ± 0.29 pmol/L High fat solid meal = 10.75 ± 0.45 pmol/L Liquid meal full-length triglycerides and intact proteins = 7.9 ± 1.25 pmol/L Liquid meal Peptamen = 1.43 ± 0.72 pmol/L ( $P < 0.05$ compared with other meals)
Shea <i>et al</i> <sup>[61]</sup>	Patients with chronic pancreatitis; healthy control subjects	Follow-up study	Consumption of 3 cans of Peptamen (the same patients completed a daily pain assessment form for 2 wk prior to initiation of enteral formulation)	8, EN evaluated within this group; 6 healthy control subjects receiving EN also evaluated	2 wk baseline period, 10 wk formula period; healthy controls evaluated on a daily basis	Chronic pancreatitis patients: Median improvement in pain scores from baseline = 68.5% ( $P = 0.011$ ) 5 of 8 patients had statistically significant decreases in pain scores Mean basal CCK levels = 0.46 ± 0.29 pmol/L Hamburger = 10.75 ± 0.45 pmol/L Ensure = 7.9 ± 1.25 pmol/L Peptamen = 1.43 ± 0.72 pmol/L ( $P < 0.0001$ compared with other meals)
Freedman <sup>[31]</sup>	Healthy volunteers	Prospective cross-over	Peptamen, one can over 2 min following an overnight fast (1/4lb hamburger; one can of Ensure)	6 (6, served as own controls)	Assessment immediately after consumption	Chronic pancreatitis patients: Median improvement in pain scores from baseline = 68.5% ( $P = 0.011$ ) 5 of 8 patients had statistically significant decreases in pain scores Mean basal CCK levels = 0.46 ± 0.29 pmol/L Hamburger = 10.75 ± 0.45 pmol/L Ensure = 7.9 ± 1.25 pmol/L Peptamen = 1.43 ± 0.72 pmol/L ( $P < 0.0001$ compared with other meals)

<sup>1</sup>Numerous results are reported within individual studies, please refer to the studies for a full summary of results. RCT: Randomized controlled clinical trial; NS: Not significant; PN: Parenteral nutrition; EN: Enteral nutrition; NJ: Nasojejunal; NG: Nasogastric; CCK: Cholecystokinin.

reduced risk of infection<sup>[27]</sup>.

In a randomized controlled trial, adult patients (age > 18 years) with acute pancreatitis were randomized to receive an EN regimen of a 100% WHP semi-elemental diet ( $n = 18$ ) through a nasojejunal feeding tube vs parenteral nutrition ( $n = 10$ )<sup>[9,33]</sup>. Overall, the authors indicated that both treatment regimens provided adequate nutritional value and did not trigger significant changes in cholecystokinin (CCK) levels, but the authors noted that patients treated with EN semi-elemental regimen demonstrated a 50% reduction in C-reactive protein, fewer septic complications, a reduction in mortality, and a marked decline in total healthcare costs when compared to patients treated with the parenteral nutrition. These studies suggest that a semi-elemental

formula confers more anti-inflammatory effects and promotes a more rapid resolution of the stress response associated with acute pancreatitis.

McClave *et al*<sup>[28]</sup> randomized patients with acute pancreatitis to receive an EN regimen of a 100% WHP semi-elemental diet through a nasojejunal tube ( $n = 16$ ) vs a parenteral nutrition ( $n = 16$ ) diet designed to provide a similar carbohydrate-to-fat ratio. While the EN regimen was shown to be as safe and effective as PN, EN was less expensive (\$761 vs \$3294). Based on these findings, it can be concluded that early EN with semi-elemental formulas may be used preferentially over parenteral nutrition among patients with acute pancreatitis due to reduced healthcare cost and improved clinical outcomes.

The effects of semi-elemental formulas appear to extend beyond patients with acute pancreatitis. Freedman<sup>[31]</sup>, in a three day crossover study among six healthy volunteers treated with a 100% WHP semi-elemental diet compared to a standard polymeric formula, reported minimal stimulation of the exocrine pancreas in the semi-elemental group as assessed by CCK levels. This clinically important observation supports the role of a semi-elemental 100% WHP formula in patients with chronic pancreatitis. Shea *et al*<sup>[6]</sup>, in a study among chronic pancreatitis patients, reported that treatment with a 100% WHP semi-elemental diet, compared with a high fat meal (hamburger) or a polymeric supplemental formula containing long-chain triglycerides and intact proteins, minimally increased plasma CCK levels, and decreased postprandial pain associated with chronic pancreatitis. Furthermore, the authors suggested that the reduction in CCK may minimize activation of pancreatic enzyme secretion during digestion, thereby minimizing stress on the pancreas during meals<sup>[6]</sup>. A case report was published of a 62-year-old male suffering from chronic pancreatitis treated with a 100% WHP semi-elemental diet. After 50 wk of follow-up, normalization of liver function tests, energy level, significant weight gain, as well as significant cost savings was observed<sup>[34]</sup>.

#### **Cerebral palsy (with gastrointestinal dysfunction)**

Studies in children with cerebral palsy and gastrointestinal dysfunction have illustrated a benefit with the use of semi-elemental 100% WHP formula on gastric emptying rates. A randomized, double-blind crossover trial was conducted to evaluate the influence of protein composition on the rate of gastric emptying in 15 children (ages 4-15 years) with cerebral palsy using gastrostomy as their main route of nutrition<sup>[35]</sup>. Each child randomly received one of four isocaloric liquid test meals that contained a standard carbohydrate and fat base plus one of four protein modules: 100% casein, hydrolyzed whey, amino acids, or 40% casein/60% whey. Based on the <sup>13</sup>C octanoic acid breath test to assess gastric emptying, the fastest emptying meal was 40% casein/60% whey (median half-emptying time = 63.3 min), followed by amino acids (74.4 min), hydrolyzed whey (82.0 min), and 100% casein (153.9 min). Faster gastric emptying, in turn, was associated with a higher prevalence of adverse postprandial symptoms such as nausea, diarrhea, sweating, and retching. Based on these results, the authors concluded that in children with cerebral palsy the protein composition of a liquid meal influences the rate of gastric emptying, which might affect postprandial symptoms. Thus, the choice of an appropriate meal formula should achieve a balance between promoting slightly delayed gastric emptying times to reduce postprandial symptoms.

In another randomized, double-blind crossover trial that enrolled 13 enterally-fed children with severe cerebral palsy, subjects received a casein-based enteral

formula for one week and either a 50% whey/50% casein whole-protein formula or a 100% WHP formula for another week<sup>[36]</sup>. The three formulas were similar with respect to calories, protein, carbohydrates, fat concentration, and osmolality. No significant differences in total gastroesophageal reflux episodes, reflux pH index, or daily stool frequency were observed between the casein and whey formulas or between the two whey formulas. As found in the study by Brun *et al*<sup>[37]</sup>, median gastric half-emptying time as measured by the <sup>13</sup>C octanoic acid breath test was faster with a whey formula (33.9 min for both whey formulas combined) than the casein formula (56.6 min). In contrast to the Brun *et al*<sup>[37]</sup>'s findings, individual and combined symptoms of gagging, regurgitation, irritability, pain, and constipation did not differ significantly between the casein and whey formulas, nor was a significant correlation observed between gastric emptying time and gastrointestinal symptoms. Overall, their study showed that children who have severe cerebral palsy had significantly faster gastric emptying with WHP compared with casein based formulas. Five of 13 children with delayed gastric emptying in the casein formula group normalized with one of the whey-based formulas leading the authors to conclude that slight acceleration in gastric emptying with whey-based enteral formula relatively to the casein formula might be beneficial in some children with severe cerebral palsy and significantly delayed gastric emptying<sup>[36]</sup>.

In a study evaluating nine consecutive outpatients with spastic quadriplegia, subjects (age range, 3-18 years) were fed a formula that contained casein (80%) and soy (20%) through a gastrostomy tube. After gastric emptying was confirmed, each patient participated in a one month, double-blind randomized controlled trial that compared the effects of the casein-predominant formula with three different whey-based formulas: (1) whey dominant; (2) whey hydrolysate; and (3) whey hydrolysate with 70% of the fat as medium-chain triglycerides. The mean percentage of gastric radioactivity at 120 min was significantly lower in the whey-predominant formulas compared with the casein-predominant formula (whey predominant = 48% ± 19%, whey hydrolysate = 56% ± 23%, whey hydrolysate with medium-chain triglycerides = 59% ± 19%; casein-predominant formula = 69% ± 14%;  $P < 0.001$ ), confirming that whey-predominant formulas provided faster gastric emptying times than casein-predominant formulas. Furthermore, there was also a reduction in vomiting episodes when the whey-based formula feedings were compared to the casein-based feedings<sup>[8]</sup>.

#### **Cystic fibrosis**

Poor growth and limited weight gain is a significant concern among persons with cystic fibrosis. Erskine *et al*<sup>[38]</sup> conducted a study among 16 pediatric patients (age range: 4 to 20 years) with cystic fibrosis who

were pancreatic insufficient and treated with either a semi-elemental 100% WHP nutritional formula without enzyme replacement vs a polymeric formula with enzyme replacement for six days. An improvement in fat absorption was observed for both groups, and no appreciable differences between groups were reported in terms of fat percentage increase (polymeric formula =  $82.3\% \pm 3.1\%$  vs semi-elemental formula =  $80.2\% \pm 2.9\%$ ). However, the patient burden could be potentially decreased with the semi-elemental formula due to the elimination of large enzyme pills that are often uncomfortable to swallow<sup>[39]</sup>. In another study among 10 cystic fibrosis patients who were undernourished, Shepherd *et al.*<sup>[39]</sup> reported that a one year course of nutrient supplementation with a 100% WHP formula resulted in long-term improvement in energy and protein intake and maintenance of net anabolism. Based on these limited studies with short-term follow-up, it still remains unclear if semi-elemental formulas provide additional benefit long-term compared to conventional polymeric formulas in this population.

### Stroke

Studies of semi-elemental formula and stroke are summarized in Table 3<sup>[40,41]</sup>. In a double-blind randomized trial of early enteral nutrition among 31 elderly patients (age  $\geq 65$  years) who were admitted within 48 h after acute ischemic stroke, 16 patients were randomized to receive five days of nasogastric feeding with a hydrolyzed casein formula and 15 were randomized to receive a 100% WHP semi-elemental diet<sup>[40]</sup>. After five days of treatment, there was no difference in mortality, lactic acid, serum albumin, and C-reactive protein between the two groups, though the study may not have been adequately powered to detect these differences. However, serum levels of interleukin-6 (a cytokine that modulates inflammation) were significantly lower and levels of glutathione peroxidase (an enzyme that scavenges free radicals) were significantly higher in the semi-elemental group<sup>[41]</sup>. Similarly, in a retrospective study of 72 severe acute stroke patients admitted to a single hospital in Japan, 37 patients began enteral nutrition with a 100% WHP semi-elemental diet within 3 d of admission, while the other 35 patients received a standard polymeric formula<sup>[41]</sup>. Baseline patient and clinical characteristics were similar between the groups. However, the in-hospital mortality rate was significantly lower among patients who received 100% WHP diet (2.7%) than those who received the standard formula (22.9%)<sup>[41]</sup>. Collectively, these results implies that enteral formula containing 100% WHP may have beneficial short-term anti-inflammatory effects than polymeric formulas in hospitalized patients with acute ischemic stroke.

### HIV

Maintaining adequate nutrition and bolstering nutritional parameters is of particular importance in persons living

with HIV. Extreme weight loss, infections, diarrhea, and fat distribution changes may occur as a result of the disease itself or because of the potential myriad of medications used to treat complications associated with HIV. In a study conducted among 23 HIV patients with chronic diarrhea, a 100% WHP semi-elemental diet was well tolerated and demonstrated a significant decrease in the number of stools compared to consumption of a regular oral diet (3.6 stools/d vs 1.1 stools/d, respectively,  $P < 0.01$ ), and a 53% reduction in fecal fat concentration ( $0.021 \pm 0.025$  g of stool,  $P < 0.019$ )<sup>[42,43]</sup>. Similarly, in 35 HIV patients suffering from malabsorption syndrome, treatment with a 100% WHP semi-elemental diet for eight weeks was effective in promoting weight gain and managing diarrhea among HIV patients<sup>[12]</sup>. In a randomized trial comparing total PN ( $n = 12$ ) and an oral semi-elemental diet ( $n = 13$ ) among HIV patients suffering from severe malabsorption, the PN group consumed more calories ( $P < 0.05$ ) and gained more weight ( $P = 0.057$ ) than patients treated with a semi-elemental diet; however, the semi-elemental group scored significantly better than the PN group on a physical functioning subscale of quality of life ( $P < 0.01$ )<sup>[44]</sup>. Collectively, these studies supports the concept that optimal use of enteral nutrition using 100% WHP formulas may improve functional status, reduce diarrhea, and reduce HIV-related cachexia.

### Critically ill and intensive care unit

In a prospective trial conducted by Borlase *et al.*<sup>[45]</sup>, hospitalized critically-ill geriatric patients (Mean age, 66 years) with compromised gastrointestinal function were given tube feeding formula for either a primary or secondary gastrointestinal disorders. Patients were randomized to receive either a 100% WHP semi-elemental diet ( $n = 8$ ) or FAA formula ( $n = 8$ ), and tolerance was evaluated in enteral tube feeding. No significant differences between the groups were observed in terms of compliance with prescribed tube feeding, caloric goals, diarrhea, or abdominal discomfort, though a higher number of stools was reported in the FAA group. Additionally, Heimburger *et al.*<sup>[46]</sup> conducted a trial among intensive care unit patients who were randomized to receive treatment with a 100% WHP diet ( $n = 26$ ) or a standard polymeric diet ( $n = 24$ ) for ten days. The authors reported increases in serum prealbumin and fibronectin in both groups but levels reached statistical significance in the 100% WHP diet group only, indicating improved nutrient assimilation in the semi-elemental group.

In a double-blind randomized trial pilot study, intensive care unit (ICU) patients randomized to enteral treatment with a 100% WHP semi-elemental diet ( $n = 5$ ) demonstrated less gastrointestinal bleeding than those receiving a standard polymeric diet ( $n = 5$ ), suggesting that a semi-elemental diet may be sufficient to reduce ICU-stressed related peptic ulcer disease without need for acid-blocking agents<sup>[47]</sup>.

**Table 3** Selected studies of semi-elemental whey hydrolyzed protein diets and stroke

Ref.	Study population	Design	Feeding mode (comparison)	No. patients (comparison)	Feeding duration	Relevant results <sup>1</sup>
de Aguilar-Nascimento <i>et al</i> <sup>[40]</sup>	Elderly patients with acute ischemic stroke	RCT	NG feeding with Peptamen (Hiper-diet Energy Plus, standard formula containing hydrolyzed casein)	10 (15)	5 d	Mortality: 3/10 in Peptamen group, 4/15 in the casein group ( $P = 1.0$ ) ICU length of stay: 16 ± 8 d in the Peptamen group, 16 ± 5 d in the casein group ( $P = 0.97$ ) IL-6 (pg/dL): Peptamen group: 62.7 ± 56.2 to 20.6 ± 10.3 Casein group: 64.3 ± 40.3 to 42.0 ± 26.7 ( $P = 0.03$ between group difference) Glutathione (U/G Hb): Peptamen group: 32.2 ± 2.1 to 39.9 ± 4.8 Casein group: 30.0 ± 5.0 to 26.2 ± 6.7 ( $P = 0.03$ between group difference) Glucose (mg/dL) Peptamen group: 132 ± 19 to 139 ± 18 Casein group: 148 ± 20 to 214 ± 43 ( $P = 0.17$ between group difference)
Miyazaki <i>et al</i> <sup>[41]</sup>	Severe acute stroke patients requiring tube feeding	Retrospective follow-up study	Peptamen through an enteral feeding tube (mein, normal protein enteral formula)	37 (35)	1 wk	In hospital mortality: 2.7% in the Peptamen group, 22.9% in the Mein group ( $P < 0.05$ ) Blood urea nitrogen (BUN, median): 35 mg/dL in the Peptamen group, 23 mg/dL in the Mein group ( $P < 0.05$ )

<sup>1</sup>Numerous results are reported within individual studies, please refer to the studies for a full summary of results. RCT: Randomized controlled clinical trial; NG: Nasogastric; ICU: Intensive care unit.

### Geriatric patients

Protein-calorie malnutrition is a common problem among nursing home residents and the aging population. Thus, Feller *et al*<sup>[48]</sup> investigated the nutritional efficacy and tolerance of two different formulas (a 100% WHP semi-elemental diet and an FAA formula) among chronically tube-fed elderly patients. Patients were started on either formula for four weeks and then crossed over to the other study formula. Overall, the 100% WHP diet was superior to the elemental diet in terms of maintaining total protein and albumin levels of the tube-feeding dependent geriatric patients. However, studies are lacking on evaluating the role of 100% WHP in the general geriatrics population with regards to maintenance of muscle mass, improvement of nutritional and functional status.

## DISCUSSION

Patients with a heterogeneous array of acute, chronic, and genetic conditions may suffer from feeding complications and as a result, may not be able to achieve or maintain adequate or appropriate energy, macronutrient, and micronutrient requirements with a standard oral diet because of difficulties tolerating, digesting, or absorbing whole foods. Fortunately, accumulating clinical evidence indicates that patients with feeding difficulties may be able to achieve improved health and nutritional outcomes through the use of 100% WHP semi-elemental diets. These types of diets, which are composed of peptides, essential fatty acids, medium chain triglycerides, vitamins, and minerals, are designed to be easily assimilated and well-tolerated. Thus, our

objective was to summarize the studies that evaluated semi-elemental WHP diets and nutritional and health outcomes among all patient populations in the scientific literature.

Overall, and as summarized above, the totality of available scientific and clinical evidence indicates that semi-elemental WHP diets are well-tolerated, digested, and absorbed among various patient groups, including those with Crohn's disease, acute and chronic pancreatitis, stroke, HIV, and critically ill. Specifically, the results across the studies show that semi-elemental WHP diets perform as well or better than comparison diets (*e.g.*, amino acid based formulas, parenteral nutrition, regular oral diets) in terms of weight gain and growth, reduction of the systemic inflammatory response, efficiency of nutrient assimilation, lower mortality rates, and lower healthcare costs. Importantly, advantages of a semi-elemental WHP diet are observed across a multitude of patient populations with various health conditions and across all age ranges. The robustness of findings across all patient groups illustrates the efficacy and effectiveness of such dietary regimens.

There are several lines of mechanistic evidence supporting a beneficial role of peptide-based hydrolyzed whey proteins for feeding and nutritional support. In a review of peptide-based diets compared with intact protein or free amino acid formulations among patients with impaired digestion or absorption, DeLegge<sup>[35]</sup> cited several potential advantages, including improved nitrogen absorption and utilization, maintenance of gut integrity, reduction of bacterial translocation, improved visceral protein synthesis, and enhanced immune support. Peptide-based formulas may facilitate an

**Table 4** Suggestions for future semi-elemental whey hydrolyzed protein diet studies

Level of study process	Suggestions for future semi-elemental WHP diet studies
Study development and initiation	Clearly defined study population with reported response rates and loss-to-follow-up data
Study development and initiation	Identification and inclusion of a study population with sufficient statistical power to determine a difference between the formulas under study. The estimated number of subjects based on power calculations should be included in the methods section
Study development and initiation	Stated goals and objectives of the analytical research. Given the multitude of possible outcomes, researchers should strive to clearly state the objective endpoints of the analysis
Analytical comparisons	Clearly define the dietary formulas and product names under study to facilitate a more complete and accurate summary of the findings across studies
Results	Present results with levels of variance such that future systematic reviews and quantitative assessments can combine data across studies
	Present results by intake level and duration of follow-up such that future assessments can evaluate quantitatively these important factors when weighing the evidence
Discussion	Identify important study design, analytical, or other research limitations and challenges so subsequent researchers can endeavor to address these challenges

WHP: Whey hydrolyzed protein.

optimum digestive process ultimately leading to an absorptive advantage compared with free amino acid and intact protein based formulas. Indeed, several studies have suggested that the majority of nitrogen from protein is absorbed as peptides and that amino acids may be absorbed more efficiently in the form of peptides than free amino acids<sup>[49-51]</sup>. Amino acids infused into the intestine in peptide form are more readily absorbed than free amino acids, secondary to the PepT1 transporter system. The PepT1 transporter is located in the microvillus membrane and has a well-established role as a transporter for di- and tri-peptides. Dietary intake and amino acid composition of the dietary protein increases the expression of PepT1<sup>[52]</sup>. Primarily, expression of PepT1 is prevalent in the small intestine, but limited in the colon. In patients with short bowel syndrome, Crohn's disease and ulcerative colitis, colonic PepT1 is increased, thereby increasing protein absorption<sup>[53]</sup>. Combined characteristics of efficient uptake of di- and tri-peptides and low osmolality may be advantageous for enteral nutrition solutions and have a significant role in nutritional management of various disease states. Furthermore, in terms of tolerance, it has been suggested that peptide-based protein may have improved nitrogen retention compared to free amino acids or intact protein, possibly resulting from the peptide's ability to enhance intestinal microcirculation, thereby improving absorption<sup>[35,54]</sup>.

In addition, several health benefits pertaining to the functional and therapeutic aspects of whey protein have been cited extensively in the literature. A growing body of studies recognizes that whey protein has a broad range of possible beneficial impacts on bone health, muscle growth, immune support, infection, wound healing, and aging<sup>[55-58]</sup>. For example, in a recently published meta-analysis of randomized clinical trials of whey protein and body composition, body weight (-4.20 kg, 95%CI: -7.67, -0.73) and body fat (-3.74 kg, 95%CI: -5.98, -1.50) were significantly decreased from baseline when whey protein was used as a meal

replacement<sup>[58]</sup>. In addition, a statistically significant increase in lean body mass (2.24 kg, 95%CI: 0.66, 3.81) was observed among studies that included a resistance exercise component along with whey protein.

Results from several experimental animal studies of semi-elemental WHP diets have augmented the evidence base of human studies. Tappenden *et al.*<sup>[59]</sup> evaluated the effects of a semi-elemental diet among piglets that underwent gastrostomy placement and banding of the superior mesenteric artery to restrict blood flow to baseline fasting levels, and found that a whey peptide-based diet stimulated the structure and function of the piglets' compromised intestines, and reduced gastrointestinal inflammation. In a study conducted by Zonta *et al.*<sup>[60]</sup>, female piglets that underwent bowel transplantation were divided into four study groups: Standard swine chow ad libitum in the postoperative period (group 1,  $n = 5$ ); polymeric enteral solution (group 2,  $n = 5$ ); and a 100% WHP semi-elemental formula (group 3,  $n = 5$ ). None of the transplanted pigs in the semi-elemental formula died before the end of the study and it was suggested that this nutritional regimen may provide faster recovery for the mucosal barrier as well as limit the hypercatabolic state. In a comprehensive animal study evaluating sepsis and septic shock pertaining to critically ill states, rats were allocated to: (1) a soy-based diet high in cysteine and crude fiber (CHOW) and devoid of EPA-DHA; (2) a whey-peptide based liquid diet high in cysteine, EPA-DHA, and FOS (CYSPUFA); or (3) a casein-based liquid isonitrogenous diet low in cysteine and devoid of EPA-DHA-FOS (CASN)<sup>[61]</sup>. Rats were fed these diets for six days following injection with lipopolysaccharide to mimic sepsis and septic shock. The CYSPUFA group lost significantly less weight (vs CASN or CHOW,  $P < 0.05$ ) and had improved levels of liver enzyme concentration, suggesting that a diet rich in CYSPUFA protects against induced systemic inflammatory responses. Previously, the authors reported that intrahepatic levels of cysteine, adenosine and

GSSG were significantly improved in rats on CYSPUFA compared with CASN ( $P < 0.05$ )<sup>[62]</sup>. Moinard *et al*<sup>[63]</sup> evaluated the role of a 100% WHP semi-elemental formula compared with the standard polymeric formula among rats with traumatic brain injury. The authors reported an improvement in glutamine concentration among rats receiving a 100% WHP formula, suggesting that the use of a semi-elemental formula may limit response to injury after suffering a traumatic brain injury<sup>[63]</sup>.

### Research gaps and advancing the science

Despite the abundance of evidence illustrating the many benefits of a semi-elemental WHP diet, several factors should be considered when interpreting the totality of evidence. This review is a comprehensive summary of findings across various patient populations, and serves as a foundation for the evidence across the total body of scientific and clinical literature. However, each patient population discussed in this summary may warrant its own specific review manuscript. To that end, future papers, whether based on data analysis or reviews of the literature, should strive to harmonize the methodological approach to critically examine the evidence.

The overall quality of evidence is strong as most studies were randomized controlled clinical trials or intervention studies conducted among various study populations. However, interpretation of findings is somewhat limited by small sample sizes and the inability for some studies to achieve statistically significant differences (if apparent) because of low statistical power. In fact, many studies evaluated analytical study populations of fewer than 10 patients. Thus, the generalizability of study findings should be made in light of possible issues with selection bias. To be sure, it is difficult to identify viable study populations given the nature of the conditions under study, such as acute illness and/or complex genetic or chronic diseases.

Future studies should attempt to standardize the study design, methodological, and analytical procedures when conducting evaluations of semi-elemental WHP diets (Table 4). Currently, a considerable amount of evidence comes from published abstracts, conference proceedings, and case studies. More analytical, peer-reviewed research studies are needed to foster more comprehensive quantitative analyses, such as meta-or pooled analyses. Thus, the consistency in the design and methodological approach with uniform results reporting is of fundamental importance to systematically summarize and interpret the evidence.

To our knowledge, this is the largest and most comprehensive summary of semi-elemental WHP diet studies conducted. Our goal was to summarize the evidence for all types of comparisons among all types of study populations. Based on this review and in terms of digestion, absorption, and tolerance outcomes, the totality of evidence from the scientific and medical

literature indicates that feeding with a semi-elemental WHP diet performs as well as or better than parenteral or amino acid based diets. In addition, other beneficial outcomes, such as improved mortality and economic advantages, have been reported. In conclusion, patient populations that have difficulty digesting or absorbing standard diets, or those who are unable to attain adequate nutrition, may be able to achieve improved health outcomes and nutritional goals through the use of semi-elemental WHP diets.

## COMMENTS

### Background

Nutrition plays a significant role in achieving optimal health, but in certain high risk populations with significant systemic illnesses, achieving adequate nutrition with a traditional oral diet maybe difficult secondary to inability to tolerate, digest, and absorb whole foods. Numerous clinical studies have demonstrated significant health benefits with semi-elemental diets in all phases of the dietary process. These studies have suggested improved growth and development patterns, fewer gastrointestinal complications, improved visceral protein levels, and decreased rates of mortality across multiple disease states.

### Research frontiers

Semi-elemental formulas have been shown to reduce the degree of regurgitation, gastric emptying times, and gagging while improving tolerance. As a result, studies have suggested improved growth and development patterns, fewer gastrointestinal complications, improved visceral protein levels, and decreased rates of mortality.

### Innovations and breakthroughs

This paper is one of the first in the literature to comprehensively summarize the role of semi-elemental formulas across various patient populations. This paper serves as a foundation for the evidence across the total body of scientific and clinical literature for the routine use of semi-elemental formulas in various nutritionally vulnerable populations.

### Applications

This paper serves as a foundation for the evidence across the total body of scientific and clinical literature for the routine use of semi-elemental formulas in various nutritionally vulnerable patient populations such as Crohn's disease, chronic pancreatitis, human immunodeficiency virus, cerebral palsy, and acute cerebral vascular accidents.

### Terminology

Semi-elemental formulas, however, contain peptides of varying chain length and primarily medium chain fatty acids. While semi-elemental diets are slightly more expensive than polymeric diets (formulas containing intact protein, complex carbohydrates, and long chain triglycerides), they are widely used because it is suggested that they are better absorbed and tolerated in patients with malabsorptive conditions and are more palatable than conventional elemental formulations.

### Peer-review

This is an excellent article. The information is extremely helpful for the practice of medicine.

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