Review

The importance of nutrition in wound management: new evidence from the past decade

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Abstract

Malnutrition is known to contribute to wound development and impair wound healing through reduction in the availability of nutrients to maintain optimal cell maintenance and repair.

This review examines studies from the last decade identified via a search of PubMed™ and systematic review databases to identify evidence for the effectiveness of nutritional interventions in wound healing. Studies reported identified via the search included 61 primary studies and six systematic reviews.

Generally, single nutrient interventions were found to be less effective than interventions utilising multiple nutrients. Immune modulating supplements containing arginine (Arg) were shown in 13 studies to result in significant improvements in at least one outcome measure for the intervention groups. There was also support for the use of arginine combined with anti-oxidant nutrients in malnourished individuals with pressure injuries (PI), and this intervention was found to be cost effective. The administration of glutamine (Gin) via the enteral nutrition (EN) route appears to convey a beneficial effect, particularly in burns and trauma patients, compared to parenteral nutrition (PN) administration. Omega-3 fatty acids were found to improve healing of diabetic foot ulcers. Encouraging further large-scale, multi-centre, prospective nutritional intervention research in areas of evidence deficiency is recommended.

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Introduction

Wound healing is an important focus of care across all settings, not limited to any particular condition or age group. Achieving optimal healing requires an understanding of nutritional requirements, and these need to be adapted to the setting and incorporated into a care plan.

The economic burden of wounds across various healthcare setting is not fully defined. This is due to a lack of centralised incidence and cost data. Chronic wounds such as pressure injuries (PIs) (also called pressure ulcers) are recognised as one of the more challenging wounds to manage for a multidisciplinary team[1]. In Australia, PIs alone have been reported to cost an estimated A$983 million for the 2012–13 fiscal year, equating to 1.9% of public hospital expenditure or 524,661 bed days from 121,645 cases[2]. The 2017 New South Wales Pressure Injury Point Prevalence Survey reported that 7.7% of inpatients had a PI, with 4% of these being hospital acquired[3]. In residential aged care facilities, 7.8% of residents had a PI, and 9.3% of community or outpatient participants reported a PI in this survey[3]. In addition, acute wounds such as postoperative wound breakdown or surgical wound dehiscence (SWD) are often under-reported and contribute significantly to the economic burden of care[4]. In the US, non-healing infected surgical wounds were the most common and costly wound type, equating to US$13.1 billion in Medicare benefits in 2014[4]. These are not only managed in the hospital setting, increasing average hospital length of stay (LOS) in the US by 9.4 days, but also in the community setting[4]. It has been reported in the UK that over 57% of SWD healing by secondary intention were managed in the community setting[4].

Risk factors for the development of wounds are complex and multi-factorial. It is recognised that unintentional weight loss is a predictor for wound development; however, this is also complicated by health co-morbidities as well as individual circumstances[5]. Elderly people living on their own are at higher risk of malnutrition. Whilst meal supports may be available, this may not supply an adequate full day's required nutritional intake, and comes at an economic burden to the individual that may be a deterrence. Additionally, physical functioning may be impaired, limiting ability to optimally prepare meals and subsequently decreasing intake. Confinement to a bed or chair is a known contributor to PI and increased mortality risk[5].

Malnutrition is known to contribute to wound development and impair wound healing through reduction in the availability of nutrients to maintain optimal cell maintenance and repair. Due to the decrease in sub-cutaneous adipose tissue in undernourishment, cushioning afforded over bony prominences is reduced, compromising the tissues ability to cope with pressure, friction and shear[1]. In addition, immunity is decreased in the undernourished, allowing infection[4]. Malnourished patients are twice as likely to develop PI (relative risk (RR) 2.1; 95% CI, 1.1–4.2)[5]. Whilst malnutrition is not commonly thought of as a condition prevalent in western countries, the Nutrition Care Day Survey completed in 2010 indicated that, from 56 participating hospitals across Australia and New Zealand, representing 3122 patients, 32% of patients were malnourished, with a further 41% identified as "at risk of malnutrition"[6].

Addressing nutrition in wound healing is a recognised part of the multi-disciplinary management required to achieve optimal healing outcomes[1,4]. Differences do exist between the nutritional management of acute and chronic wounds; however, there are many similarities[1,4]. Nutrition for wound healing is often described in terms of the provision of macronutrients, micronutrients and fluid (water). Macronutrients are probably the most commonly known group of nutrients and are considered as important for their role in wound healing, with the three pillars of protein, fats and carbohydrates falling under this umbrella term. Protein as a whole is considered the 'building block' of muscle or lean tissue for the body, as well as for cells required for optimal immune function (lymphocytes, leukocytes, phagocytes, monocytes and macrophages) and the wound healing protein collagen[7]. As part of normal digestion it is broken down into amino acids, of which some are non-essential (able to be produced by the body), some are essential (required to be provided through nutritional intake in adequate amounts), and some are conditionally essential[8].

Conditionally essential amino acids are of particular interest in wound healing. Conditionally essential amino acids are those which, under normal physiological circumstances, are available in adequate volumes within the body to achieve healthy homeostasis; however, in periods of stress, additional exogenous sources are required to maintain optimal function[9]. Such examples regarding wound healing in the reported literature are Arg, Gln and methionine. Arg is a precursor for proline, glutamate and polyamine synthesis[10]. It has been demonstrated to promote wound healing, stimulate insulin, insulin-like growth factor-1 and pituitary human growth hormone. In-vitro studies have also demonstrated that it has a role in the promotion of T-cell proliferation[10]. Gln acts as a direct source of cellular energy to assist with metabolic functions as a nitrogen shuttle. Gln stimulates immune function and wound healing through acting as a fuel source for lymphocytes, macrophages and fibroblasts[10]. Importantly, Gln preserves gut integrity through acting as a primary fuel source for the enterocytes and colonocytes within the gastrointestinal tract which may prevent translocation of pathogenic bacteria across the intestinal lumen, in turn preventing systemic infections[10]. Gln is an important nutrient in the support of anti-oxidant function through its role as a precursor for glutathione and potentially reduces insulin resistance[10].

During times of physiological stress, synthesis of nucleotides is down-regulated in the body, resulting in decreased replication of rapidly dividing cells required for wound healing and immunity, such as GI mucosa, lymphocytes and macrophages[11]. One area of research relating to wound healing is the exogenous supplementation of RNA nucleotides in combination with other active nutrients[11].

Upon intake, fat is broken down into smaller components known as fatty acids which, similar to protein, are regarded as essential and non-essential, and cholesterol[8]. Fatty acids themselves are essential in the body to form the lipid bi-layer of all cell and organelle membranes as well as the membranes that insulate nerve axons. Fats also provide a source of cellular energy via beta oxidation during catabolic states[8]. Similar to protein, certain subgroups of fatty acids have been researched with specific interest related to wound healing. For example, the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are metabolised to comparatively less inflammatory and less immunosuppressive metabolites than omega-6 fatty acids[11] and this in turn may aid wound healing. Carbohydrates, specifically glucose, are the preferred substrates for cellular energy, especially for brain and erythrocytes. Current recommendations for a healthy diet are that 45-65% of energy be provided through carbohydrates (Australian Dietary Guidelines, available from: https://www.health.gov.au/resources/publications/the-australian-dietary-guidelines).

Micronutrients is the group terminology for nutrients that are present in the body in minute amounts but contribute to essential function and optimal homeostasis. This grouping is made up of vitamins, minerals and trace elements. Micronutrients provide co-factors for many necessary enzymatic processes in the body. Some micronutrients, especially fat soluble nutrients, have good reserves in the body when dietary intake is adequate in a healthy state; however, water soluble nutrients are not stored in the body and regular intake is essential for healthy functioning. During periods of stress, including that of wound healing, their intake becomes more essential.

Ascorbic acid, or Vitamin C, is possibly the most well recognised micronutrient in regards to is contribution to wound healing and immunity. Vitamin C acts as an anti-oxidant as well as being essential for collagen production in wound healing through its role as a co-factor during collagen synthesis. Similarly to Vitamin C, zinc is well regarded for its role in immune functions and wound healing[12]. Deficiency of zinc leads to suppression of cell proliferation as it is a co-factor for many enzymes required for the synthesis of RNA, DNA and proteins[13,14].

Iron also has an essential role in wound healing as an essential part of haemoglobin which is required for oxygen transport to the regenerating wound tissue[12,15]. In addition, iron is a co-factor in the enzymatic process required for synthesis of collagen[15,16]. Emerging areas of research regarding wound healing include vitamin D, calcium b-hydroxy-b-methylbutyrate (CaHMB), probiotics, bioflavonoids and folate; however, their roles are currently less well understood[17–22].

Nutrients investigated for their role in wound healing have traditionally been supplemented as an individual or single nutrient supplementation strategy or in addition to other nutrients which may convey their own beneficial effect on wound healing as a combined nutrient supplementation strategy. Alternate nutritional interventions have also been reported where interventional strategies employed are not able to be assigned to either of the first two categories.

The aim of this review is to summarise the readily accessible evidence from the past decade that addresses nutritional interventions in wound healing.

Methods

A literature review was conducted using the online database PubMed™ to identify studies published in the past 10 years that evaluated the effect of nutritional interventions on wound healing outcomes. PubMed™ was utilised due to its easy and free accessibility for clinicians, regardless of organisational affiliations. This interface searches the same Medline content as Ovid; however, it does not require subscription and includes all references as soon as they are added to the US National Library of Medicine (NLM) without delay. Search terms included nutrition, vitamin, mineral, protein, amino acid, arginine, glutamine, fat, carbohydrate, zinc, iron and wound. In addition, to identify any systematic reviews related to this topic, a search was conducted of systematic review databases including The Cochrane Database, Joanna Briggs Institute Database of Systematic Reviews and Implementation Reports as well as PubMed™. Search parameters were limited to human trials, English language articles and publication date (defined for the purpose of this review as 1 January 2010 to 17 January 2020). Studies published earlier to this date range were included for presentation only where they were presented as part of a systematic review published within the specified date range for the search.

Interventions considered for inclusion were nutritional interventions including parenteral (PN), enteral (EN) or oral nutrition (ON) strategies. Outcome measures of interest to this study included wound healing, anastomosis integrity, LOS and mortality. Where included systematic reviews reported on alternate outcomes of interest than this review, this data was excluded from reporting. For the purpose of this review, studies investigating topically applied nutrients/dressings, preventative administration of nutrition prior to radiotherapy, nutritional strategies to prevent wound development, study protocols, radiotherapy-induced skin/mucous membrane conditions (dermatitis, mucositis), and pharmaceutical nutritional adjuncts (such as human growth hormone and anabolic steroids) were excluded. All citations retrieved from database searches were exported into the bibliographic citation management software EndNote® X9 (Thomson Reuters). After removal of duplicates and screening of titles and abstracts against eligibility criteria for the review, potentially relevant full text articles were retrieved and assessed for their suitability for inclusion in the review.

Results

The full process of study selection is detailed in Figure 1. The results are broken down into three categories – single nutrient supplementation strategies, combined nutrient supplementation strategies, and alternate nutritional intervention strategies. These are considered in detail, in particular relation to their role in wound healing.

Single nutrient supplementation strategies and their role in wound healing

Arginine

Three studies identified via our search strategy investigated the amino acid as a single nutrient intervention strategy in wound healing (Table 1)[24–26]. Debats and colleagues[24] investigated the use of 30g intravenous (IV) Arg supplementation for 5 days post-autograft reconstructive surgery vs an isonitrogenous control and demonstrated no significant difference on wound healing outcomes[24]. Two studies from Spain investigated the effect of EN supplementation of high dose Arg (20g and

18.9g per day) compared to lower dose Arg (12.3g per day) supplementation on wound healing outcomes following head and neck cancer surgery[25,26]. Both of these studies demonstrated significantly less wound fistula formation in the high dose intervention groups (p=0.033 & p=0.006, respectively); however, no significant differences were seen in the rate of wound infections nor LOS[25,26].

One systematic review identified[27] included one study assessing the effectiveness of arginine butyrate administered parenterally on leg ulcer healing in patients with sickle cell disease. There was a non-significant difference in incidence of complete ulcer closure reported in the Arg butyrate group (30%, 11 of 37 ulcers) versus the control group (8%, two of 25 ulcers) (p=0.056). This study also reported an improved rate of healing as determined by the mean decrease in pressure ulcer size with Arg butyrate administration compared to the control; however, the relative effect was not estimable in the systematic review and this study was assigned a very low quality of evidence due to inconsistencies with randomisation of its small cohort (62 ulcers) and its lack of statistical power to determine an effect.

Glutamine

There were two studies identified investigating the supplementation of Gln as a single nutrient intervention strategy (Table 2)[28,29]. Perez-Barcena and colleagues[28] investigated the use of IV Gln for 5 days in the intensive care unit (ICU) following multi-trauma admission. No effect of supplementation was demonstrated on mortality, LOS nor infectious complications[28]. In contrast, the study reported by

Figure 1. Flow chart of literature review process (adapted from PRISMA flow diagram[23])

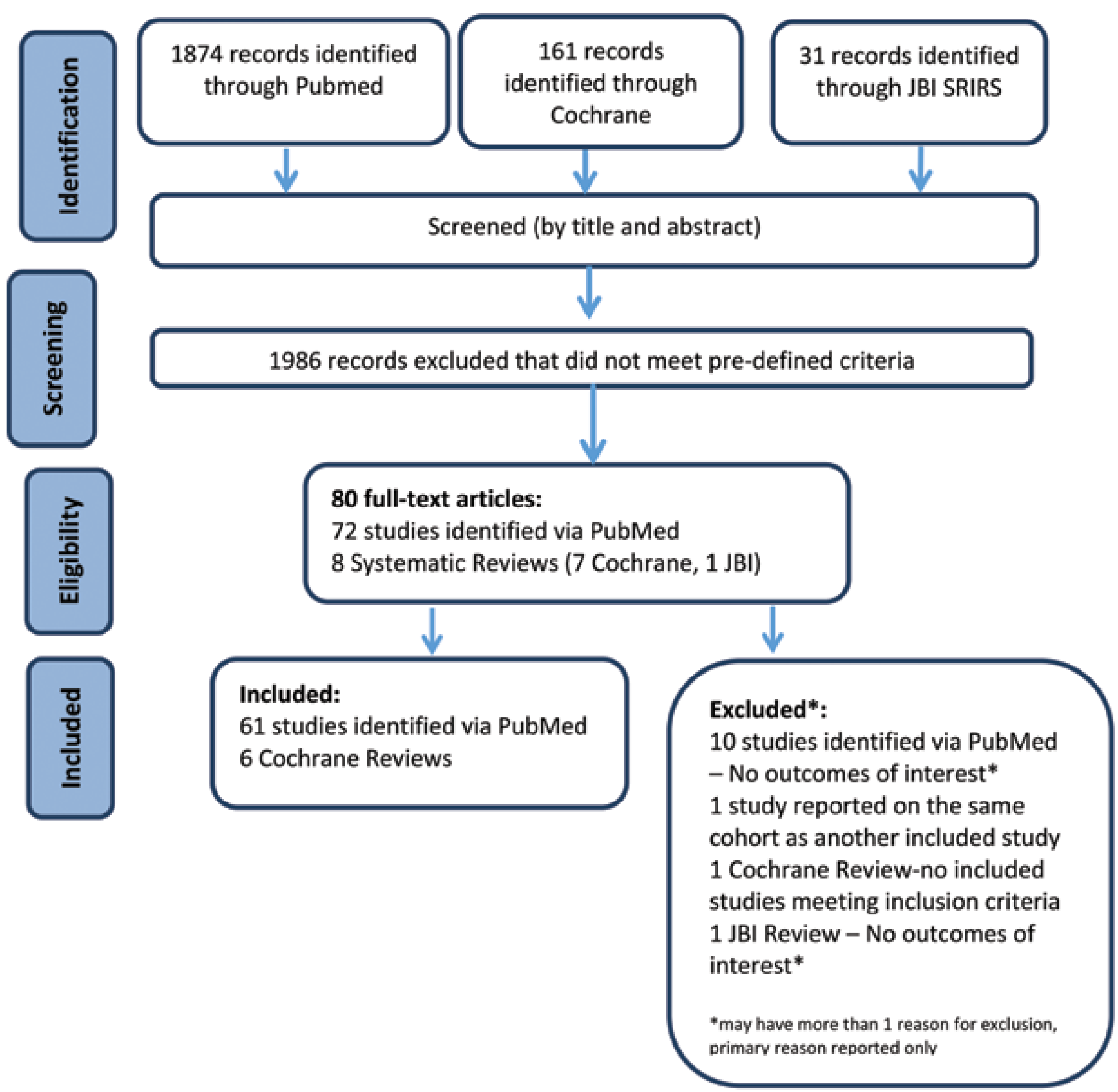

Table 1. Arginine: characteristics of included primary studies

Author/ year	Methods	Setting	Patient characteristics	Age (years±SD)	Sample size	Treatment	Comparator	Outcomes	Results
Debats, 2011[24]	DBRCT	Netherlands, University Hospital. Recruited Jul 2006 to Jul 2009	Received autografting as part of reconstructive surgery	Intervention: 42.3 (±4.2). Control: 44.6 (±4)	40 allocated	IV Arg for 5 days starting day of surgery (providing 30g Arg, 45.7mmol/l net Nitrogen, 120kcal), n=16	Isovolumetric, isonitrogenous placebo, Alanine (providing 44mmol/l net N, 100.8kcal), n=19	Wound healing (angiogenesis & reepithelialisation)	No significant difference in either wound healing measure between groups at day 5 and 10
De Luis, 2010[25]	DBRCT	Spain, Dept Otolaryngology, University Hospital, Jan 2007 to Nov 2009	Head & neck cancer (squamous cell carcinoma), eligible for major ablative surgery	Mean 62.6 (±11.7)	115	High dose Arg via EN (20g/day), commenced within 24hrs of surgery, fed for ~15 days per hospital protocol (min 10 days EN support), n=58	Medium dose Arg via EN (12.3g/day), n=57	Postop complications (general infections, fistula, wound infections), LOS	Sig less fistula detection in high and medium dose Arg groups than low dose group (p=0.033), no difference in general or wound infections, Trend towards lower LOS in higher Arg group<medium Arg group<low Arg group (p=0.034)
De Luis, 2015[26]	RCT	Spain, Dept Otolaryngology, University Hospital, 2009–2011	Head & neck cancer (squamous cell carcinoma), eligible for major ablative surgery	Mean 61.9 (±10.7)	84	High dose Arg via EN (18.9g/day), commenced within 24hrs of surgery, fed for ~10 days per hospital protocol , n=28	1. Medium dose Arg via EN (12.3g/day), n=28. 2. Low dose Arg via EN (5.7g/day), n=28.	Postop complications (general infections, fistula, wound infections), LOS	Sig less fistula detection in high dose Arg group (p=0.006), no difference in general or wound infections, no difference in LOS

Blass and colleagues[29] investigated EN supplementation of Gln, in addition to other anti-oxidant nutrients, and a high protein diet in trauma patients who had demonstrated delayed wound healing. This study demonstrated a significant improvement in time to wound healing (p=0.01); however, no effect on LOS was seen[29].

In the systematic review conducted by Tan and colleagues[30] investigating the effects of immunonutrients following burn injury, seven studies were identified that investigated the supplementation of Gin vs a control or placebo. All of these included studies were published between 2001 and 2004[30]. Three of the included studies reported on all-cause mortality following supplementation and, when pooled in the systematic review, showed a significant decrease (RR 0.25 (95% CI 0.08 to 0.78) p=0.02)[30]. All of the seven included studies reported on LOS, representing 255 participants[30]. When pooled, these results demonstrated a significant decrease in LOS (RR –5.65 (95% CI –8.09[1,31] to 3.22) p=<0.0001)[30]. It should be noted that these analyses included studies where Gin supplementation was via the EN or PN routes, and results may differ for these methods of administration.

This systematic review also included three studies investigating the effects of ornithine α-ketoglutarate (a precursor for Gin and Arg) vs soy protein or placebo[30]. All three studies, representing 155 participants, reported on mortality and, when pooled, results demonstrated no significant effect of supplementation (RR 0.93 (95%CI 0.37 to 2.36) p=0.88)[30]. One included study (n=48) reported on LOS and failed to demonstrate a significant decrease (RR –4.21 (95% CI –18.87 to 10.45) p=0.57)[30].

Omega-3 fatty acids

Three studies were identified that investigated the supplementation of omega-3 fatty acids from fish oil sources[32–34], although two of these studies[32,33] reported on different outcomes from the same cohort of study participants so have been combined for the presentation of outcomes in Table 3[32–34]. Two study cohorts were administered EN enriched with fish oil compared to standard EN formulas[32–34]. The study by Tihista and colleagues[34] in burn injury patients requiring mechanical ventilation demonstrated a significant decrease in sepsis (p=0.03); however, no difference in LOS was seen[34]. The cohort presented by Theilla and colleagues[32,33] investigated PI patients in the ICU. This group demonstrated a deterioration in PI state in the control group, whilst the intervention group PI severity did not change significantly.

An additional double blind, randomised controlled trial (DBRCT) by Soleimani and colleagues[35] investigated the supplementation of omega-3 fatty acids derived from flaxseed oil (100mg/day, give twice daily for 12 weeks), versus a placebo in 60 patients with grade III diabetic foot ulcers. They reported that supplementation significantly reduced ulcer length (p=0.03), width (p=0.02) and depth (p=0.01) compared to the placebo[35].

In the systematic review identified by Tan and colleagues[30], only one study investigating the effect of omega-3 fatty acids following burn injury was included. This study was published in 1995 and included 25 participants. No significant effect was seen on mortality (p=0.41); however, a decrease in LOS was reported (RR –21.0 (95% CI –41 to –0.97) p=0.04)[30].

Zinc

One small primary study was identified that investigated the role of zinc supplementation as a single agent on wound healing outcomes in a cohort of 58 patients[36]. Momen-Heravi and colleagues[36] supplemented patients with grade III diabetic foot ulcers with 220mg zinc (50mg elemental zinc) daily for 12 weeks in a DBRCT, placebo controlled study. They reported a significant increase in serum zinc levels (p<0.001), and a significant decrease in ulcer length (p=0.02), width (p=0.02), but not depth (p=0.05) in the intervention group compared with the placebo group[36]. Significant improvements in serum insulin (p=0.009), HbA1c (p=0.01), total anti-oxidant capacity (p<0.01) and total glutathione status (p=0.006) were also reported benefits with supplementation[36].

Two additional studies identified investigated the supplementation of a carnosine zinc complex (Polaprezine) in adult patients with PIs[37,38]. Both studies reported significant improvements with Polaprezine supplementation at 150mg/day compared with no supplementation on wound healing from baseline until week 8 of supplementation (p=0.009[37] and p<0.001[38]). Neither study was blinded nor randomised, and both studies consisted of small cohorts and were conducted by the same authors at the same site[37,38].

Two systematic reviews were identified that included the investigation of zinc sulphate supplementation on PI[39] or arterial and venous leg ulcer[40] healing. Only eight trials were identified between the two reviews, representing 217 total participants, all conducted prior to 1980. All included studies were identified as having risk of bias. No beneficial effects of supplementation were identified by either review[39,40].

Vitamin D

Three studies identified as part of this review supplemented with vitamin D versus placebo[20,41,42], whilst a fourth study provided a nutritional supplement fortified with vitamin D, calcium b-hydroxy-b-methylbutyrate (CaHMB) and protein versus a standard diet[19].

Razzaghi and colleagues[41] investigated the supplementation of 50,000 IU of vitamin D every 2 weeks versus placebo, over a 12-week period in 60 participants with grade III diabetic foot ulcers. This study reported an overall positive effect on wound healing with supplementation by demonstrating a significant decrease in the length (p=0.001), width (p=0.02) and depth (p<0.001) of the ulcers[41].

Burkiewicz and colleagues[20] investigated the supplementation of 50,000 IU of vitamin D every week for 2 months versus no supplementation in 52 vitamin D deficient participants with chronic venous leg ulcers. A non-significant trend towards improved healing with supplementation was reported (p=0.0676)[20].

In the DBRCT presented by Gottschlich and colleagues[42] vitamin D supplementation (100 IU/kg/d vitamin D2 in 18 patients or 100 IU/kg/d vitamin D3 in 15 patients) was compared to a control group (17 patients) following severe paediatric burn injury. No difference in LOS, number of surgical procedures, nor mortality was identified[42].

The randomised control trial (RCT) reported by Ekinci and colleagues[19] investigated the use of a diet supplemented with specialised wound healing supplements (enriched with 3g CaHMB, 1000 IU vitamin D, and 36g protein) vs a standard diet alone in 75 postoperative hip fracture patients. Supplementation was reported to significantly decrease wound healing time (p=0.037); however, no differences in LOS were observed between groups (p=0.76)[19].

Vitamin C

One study identified by Li and colleagues[43] investigated the supplementation of oral vitamin C for 7 days post dental implant surgery in 128 participants on wound healing outcomes compared to no supplementation. They demonstrated that patients who received dental implants supported with a guided bone regeneration (GBR) technique and implants for chronic periodontis had significantly improved wound healing outcomes (p<0.002) compared to no supplementation[43]. Patients who underwent implants and Bio-Oss collagen grafts and dental implants without grafts or periodontis did not demonstrate any significant benefit from supplementation[43].

Magnesium

Two studies identified investigated the effect of magnesium supplementation either alone or combined with other nutrients on wound healing outcomes[44].

In the DBRCT conducted by Razzaghi and colleagues[44], 70 participants with grade III diabetic foot ulcers were administered either 250mg/day of magnesium or placebo. Supplementation was reported to significantly decrease ulcer length (p=0.01), width (p=0.02) and depth (p=0.003)[44].

Also investigating the effects of nutritional supplementation of grade III diabetic foot ulcer healing, Afzali and colleagues[45] supplemented 57 participants with either 250mg/day of magnesium combined with 400 IU vitamin E/day or placebo for 12 weeks. This intervention was also reported to significantly reduce ulcer length (p=0.003), width (p=0.02), and depth (p=0.02) compared to the placebo group, although the mix of nutrients makes it difficult to determine if this effect was related to either nutrient alone or the combination[45].

Table 2. Glutamine: characteristics of included primary studies

Author/ year	Methods	Setting	Patient characteristics	Age (years; range)	Sample size	Treatment	Comparator	Outcomes	Results
Perez-Barcena, 2014[28]	Multi-centre DBRCT	ICU, Spain. Four centres, Oct 2010 – Oct 2012	18–75 years old, admitted to ICU with multi-trauma, requiring EN &/or PN. Caloric goal 28kcal/kg/day, protein (excluding Gln) 1–2g/day	Intervention: 43 (30–59). Comparator: 39 (28–52)	142	L-analyl-L-glutamine dipeptide 0.5g/kg body weight/day (=0.35g L-Gln/kg/day) IV via continuous infusion, for 5 days: n=71	Normal saline placebo, for 5 days; n=71	New infections within 14 days post-randomisation, ICU & LOS, mortality	No effect on mortality, LOS, infections
Blass, 2012[29]	DBRCT	Germany, Orthopaedics & Trauma, Oct 2007 – Nov 2008	Adult trauma patients with delayed wound healing (failure to heal within 10 days), Caucasian	Intervention: 45 (36–76). Comparator: 46 (27–56)	20	Protein rich diet + 2x sachets Gln Plus/day (500mg ascorbic acid, 166mg alpha-tocopherol, 3.2mg beta-carotene, 100micro g Selenium, 6.6mg zinc, 20g Gln) mixed with fluid (food/drink), n=10	Protein rich diet + isoenergetic sachets (maltodextrine), n=10	Wound healing time, LOS	Significant shorter time to wound healing (p=0.01) in intervention group, no effect on LOS

Table 3. Omega-3 fatty acids: characteristics of included primary studies

Author/ year	Methods	Setting	Patient characteristics	Age (years±SD)	Sample size	Treatment	Comparator	Outcomes	Results
Tihista, 2018[34]	DBRCT	ICU, Uruguay	≥18 years, burns ≥15% TBSA, inhalation injury, requiring mechanical ventilation for ≥6 days, exclusive EN for ≥6 days	Intervention: 38.7 (± 16) Control 41.6 (±16.6)	92	Low fat EN where 50% of fat content was replaced with fish oil rich in n-3 poly-unsaturated fatty acids. n=47	Standard low-fat EN (sunflower oil). n= 45	Infectious complications, LOS (days), mortality	Lower frequency of sepsis (p=0.03) in intervention group, trend toward overall lower infectious complications. LOS (mean 7 days lower, median 1 day higher, p=0.53)
Theilla, 2012[32, 33]	RCT	ICU, Israel	Adults, admitted to ICU with or developed ≥1 grade II PI and expected to require ≥5 days EN	Intervention: 49.3 (±20.7) Control 53.1 (±19.3).	40	Fish oil & micronutrient enriched formula (Oxepa, Abbott). n=20	Iso-nitrogenous control (Jevity, Abbott). n=20	PUSH score, LOS (hours)	Non-significant difference in PI score at baseline, PUSH score increased significantly over time in control group (p=0.02) but no significant changes in intervention group. No difference in LOS

Combined nutrient supplementation strategies and their role in wound healing

The largest grouping of supplementation type identified as part of this review was the supplementation of Arg in conjunction with other macro and micronutrients as part of immunonutrition regimens, delivered via various EN and ON preparations, with 16 studies identified (Table 4)[46–61].

Eight of the studies investigating immune-nutrition strategies identified studied cohorts of patients presenting with PI, venous ulcers or diabetic ulcers[46–52,61]. The remaining eight studies investigated outcomes for patients undergoing surgery for various malignancies[53–60].

In 13 studies where an immune modulating supplement containing Arg was compared to a standard or placebo control with no or very low levels of Arg, significant improvements were seen in at least one outcome measure for the intervention groups[47–50,52–57,59–61]. In two studies where no effect was seen in the whole cohort, when adjusted for nutritional parameters, patients with poorer nutritional indices (severe weight loss or hypoalbuminaemia) demonstrated significant improvements in outcome measures compared with controls[51,58]. This effect was not seen in the study by Leigh and colleagues[46]. This study compared a high dose of Arg (9g/day) supplementation with a moderate dose Arg (4.5g/day) supplementation in non-healing PI patients. Both groups demonstrated significant improvements in wound healing outcomes with supplementation, whilst well-nourished patients demonstrated a trend towards improved healing rates compared to malnourished patients (p=0.057)[46]. The high dose supplementation group did meet significantly more of their energy (p=0.008) and protein (p=0.008) intake compared with the moderately supplemented group, with no difference in weight change seen over the study period[46].

The cohort of 200 malnourished adults with stage II–IV pressure ulcers in long-term and home care services presented by Cereda and colleagues[47] provided a mixed nutritional supplement containing Arg and anti-oxidant nutrients compared to an isocaloric, isoitrogenous control. Supplementation demonstrated a significant decrease in pressure ulcer area (60.9%) compared to control (45.2%) (p=0.017). Both intervention and control demonstrated significantly improved wound healing (p<0.001)[47]. Interestingly, this group provided a later economic evaluation of this study[62]. This demonstrated that although the intervention supplement was significantly more expensive that the comparator (p<0.001), the intervention resulted in significant savings overall from the non-nutritional costs of care (p<0.001) [nursing p=0.001, dressings p=0.024], and significantly lower costs of PI care overall (p=0.013)[62].

In the systematic review conducted by Langer and Fink[39], seven studies (including the studies by van Anholt et al.[48] and Ohura et al.[63] identified in this literature search, with the remainder published prior to our search date criteria) were identified investigating mixed nutritional supplements compared to other nutritional interventions, and four trials (again including van Anholt et al.[48]) were identified comparing Arg-enriched mixed nutritional supplements against a standard hospital diet. When pooled, Arg-enriched mixed nutritional supplements improved Pressure Ulcer Scale for Healing (PUSH) score when compared to the standard hospital diet (p=0.0001). This analysis was limited by the small number of participants in the three individual studies included (n=80). Two studies were pooled regarding the outcome measure of ulcer size, representing 71 participants. This analysis favoured the effect of supplementation on ulcer size; however, the overall effect was not significant (p=0.14). This lack of significance is likely due to the small sample sizes in both included studies, identified in the review as being statistically underpowered, as well as their large confidence intervals.

In the systematic review conducted by Tan and colleagues[30], four studies (published prior to 2010) were identified that investigated the effects of combined immunonutrients vs multi-nutrient supplementation or placebo following burn injury. All four studies, with a total of 163 participants, reported on mortality as an outcome measure[30]. When pooled, there was no significant effect of supplementation seen (RR 1.1 (95%CI 0.47 to 2.6) p=0.83)[30]. Three of the included studies reported on LOS; when pooled, these also failed to demonstrate a significant effect with supplementation (RR 1.93 (95%CI –4041 to 8.28) p=0.55)[30].

Probiotics

Three studies identified through the review search strategy investigated the effect of probiotic administration on wound healing outcomes.

The DBRCT conducted by Kotzampassi and colleagues[21] investigated supplementation with a probiotic regimen on outcomes following elective open colonic resection with primary anastomosis for colorectal cancer. Participants (n=164) were assigned to a probiotic regimen consisting of a pre-operative loading dose of four capsules followed by one capsule twice daily orally for 15 days or placebo[21]. The probiotic capsules contained four active strains consisting of *Lactobacillus acidophilus* 1.75x 10^9cfu, *Lactobacillus plantarum* 0.5x 10^9cfu, *Bifidobacterium lactis* 1.75x 10^9cfu, *Saccharomyces boulardii* 1.5x 10^9cfu[21]. Probiotic supplementation was reported to significantly decrease overall complications (p=0.01), infectious complications (p=0.009), anastomotic leak (p=0.031), and LOS (although this data was not provided by authors)[21].

In the DBRCT, placebo controlled study conducted by Mohseni and colleagues[17], the effect of a probiotic regimen was investigated on wound healing outcomes in 60 grade III diabetic foot ulcer patients. A probiotic capsule containing *L. acidophilus*, *L. casei*, *L. fermentum*, *B. bifidum* (2x 10^9cfu/g each) or placebo was provided daily for 12 weeks[17]. Supplementation was reported to significantly decrease in ulcer width (p=0.02), length (p=0.01), and depth (p<0.02)[17].

Table 4. Combined Arg containing supplements with other active nutrients: characteristics of included primary studies

Author/ year	Methods	Setting	Patient characteristics	Age (years±SD)	Sample size	Treatment	Comparitor	Outcomes	Results
Leigh, 2012[46]	RCT	Tertiary health service, Australia	Inpatients with stage II–IV non-healing PI consuming oral diet and not on Arg supplementation	Intervention: 67.5 (±4.9). Comparator: 69.8 (±5.2)	23	Arg 9g/day (2x sachets Arginaid powder = 4.5g Arg, 4g CHO, 155mg Vit C, 40.5mg Vit E each). n=11	Arg 4.5g/day (1x sachet Arginaid). n=12	PUSH score, Nutritional status (SGA), dietary adequacy	Sig decrease in PUSH score over time in both groups (p<0.001), no difference in healing rates. Well nourished patients had trend towards greater improvement in healing rates than malnourished patients (p=0.057). No significant difference in healing rates based on Arg dose (p=0.393), patients in 9g Arg group met significantly more energy (p=0.008) and Ptn (p=0.008) reqts. No significant weight change in either group.
Cereda, 2015[47]	Multi-centre DBRCT	7 sites, Italy, between Feb 2010 – Nov 2012	Malnourished, adult long-term care residents or patients receiving home care support services presenting with stage II–IV PI; if multiple, most severe selected	Intervention: 81.1 (±10.8). Comparator: 81.7 (±10.7)	200	Ad libitum food intake + 400mL (4x100mL bottles between meals) HPE+Arg+AOx ONS (Cubitan) (500kcal, 40gPtn, 6g Arg, 18mg zinc, 128mcg Selenium, 76mg Vit E, 500mg Vit C), for 8 weeks or until complete healing or withdrawal, n=101	Ad libitum food intake + 400mL (4x100mL bottles between meals) HPE ONS (500kcal, 40gPtn, 0g Arg, 9.2mg zinc, 44mcg Selenium, 9.2mg Vit E, 76mg Vit C), for 8 weeks or until complete healing or withdrawal, n=99	% change in PI area at 8 weeks, complete healing, wound infection, % change at 4 weeks	Overall Treatment effective for both experimental and control groups in improving PI healing (p<0.001). At 8 weeks mean reduction in PI size was 60.9% in intervention group compared to 45.2% in control group (p=0.017). Non-sig decrease in intervention group towards complete healing (p=0.097). No sig diff between groups in regards to reduction of area at 4 weeks (p=0.149), and in regards to wound infections (p=0.83)

Table 4 continued. Combined Arg containing supplements with other active nutrients: characteristics of included primary studies

Author/ year	Methods	Setting	Patient characteristics	Age (years±SD)	Sample size	Treatment	Comparitor	Outcomes	Results
van Anholt, 2010[48]	Multi-country DBRCT	Healthcare centres, hospitals, long-term care facilities. Czech Republic, Belgium, Netherlands, Curacao	Well-nourished patients, 18–90 years old, receiving standard care for stage III-IV PI and standard diet without nutritional supplementation for at least 2 weeks prior to the study	Intervention: 76.2 (±3.2). Comparator: 73.0 (±3.3)	47, 43 in intention to treat analysis	ONS enriched with Arg, AOx, micronutrients (Cubitan) 3x 200mL/day (750kcal, 85.2g CHO, 60g Ptn, 9g Arg) for up to 8 weeks. n=22	Placebo – non-caloric. n=21	Change in pressure ulcer surface area, PUSH Score, length, weight, BMI, Malnutrition Universal Screening Tool (MUST) score, blood parameters	Decline in pressure ulcer size in the ONS group differed sig from control over 9 weeks (p=0.006). PUSH scores improved Sig in ONS group compared with control (p=0.011). Significant decrease in number of dressing changes in ONS group compared to control (p=0.003), significantly less time spent on dressing changes in ONS group (significant change over time, p=0.006), Mean ONS intake 75.8(±3.7)% vs control 86.5(±2.3)% (p=0.042). No significant difference in activity levels, mobility. No significant difference in blood parameters except for Vit C levels increased sig in ONS group compared to control (p=0.015). No significant differences in BMI, gastrointestinal intolerance (except for constipation , n=4 in ONS group). Average healing rate:ONS; 0.26cm^2/day over first 3 weeks then 0.16cm^2/day. Control; 0.14 and 0.15cm^2/day respectively.
Wong, 2014[49]	DBRCT, placebo controlled	Changi General Hospital, Singapore	Asian cohort, stage II–IV PI with no observable improvement in wound characteristics	Intervention: 79.4 (±5.74). Comparator: 75.5 (±3.19)	26	2x sachets of Abound ™ (7g Arg, 7g GLN, 7.9g CHO, 1.5g calcium HMB, 200mg calcium each sachet)/day for a minimum of 2 weeks. n=11	2x sachets of identical appearing placebo (CHO and calcium). n=12	Wound healing (wound area, PUSH score). Nutritional status (SGA, MUAC (Mid Upper Arm Circumference)	Length of supplementation (range) 14–38 days. No significant difference in wound size change between groups, significant increase in viable tissue in intervention group wound compared to control (p=0.02). No difference in PUSH scores between groups. No significant difference in nutritional intake (Kcal & Ptn) between groups

Table 4 continued. Combined Arg containing supplements with other active nutrients: characteristics of included primary studies

Author/ year	Methods	Setting	Patient characteristics	Age (years±SD)	Sample size	Treatment	Comparitor	Outcomes	Results
Banks, 2016[50]	RCT, pilot	Brisbane, tertiary referral hospital	Inpatients with existing or acquired stage II–VI PI	Intervention: 62.3 (±20.7). Comparator: 65.8 (±15.8)	50 randomised, 31 completed	Intensive individualised nutritional care provided by research dietitian (at least 3 x/week), HPE diet +/– ONS + Wound healing ONS containing Arg, Vit C, zinc (participants offered two different brands based on preference and prescribed per manufacturer recommendations), n=14	Standard nutritional care provided by clinical team, standard or HPE diet +/– ONS +/– EN, n=17	Energy & ptn intake, nutritional status (SGA), PUSH score, PI change from baseline, LOS	No difference in energy or Ptn intake between groups, Significantly higher Arg intake in intervention group (p<0.05), significant positive improvement on nutritional status in intervention group (p<0.05), Non-significant greater reduction in median PUSH raw score. Non-significant trend to greater PI area % change reduction in intervention group.
Brewer, 2010[61]	Quasi controlled trial	Melbourne, spinal outreach risk reduction service	Spinal cord injury, Grade II, III, IV PI, >18 years, predominately well nourished	Intervention: 52.2 (±2.7). Comparator: 49.9 (±4.1)	18	2x sachets Arginaid powder/day (9g Arg, 8g CHO, 310mg Vit C, 120mg Vit E), until full wound healing as assessed by spinal nurse, n=18	Historical control of patients from service database with PIs over the previous 3 years, with adequate documentation, n=17	PI healing (PUSH score, time to healing)	Significant decrease in time to healing for all PIs in the intervention group compared with control (p=0.006)
Armstrong, 2014[51]	Multi-centre DBRCT	38 hospitals and wound care centres in USA, Europe, Taiwan	Community dwelling, type 1 or type 2 diabetes undergoing pharmacological treatment for glycaemic control, at least 1 grade 1A foot ulcer (University of Texas criteria)		271	Arg 7g, 7g Gln, 1.2g ß-hydroxy-ß-methylbutyrate, 79kcal (Juven/ Abound) supplement drink, x 2/day for 16 weeks, n=129	Control supplement, low Glycaemic Index, 88kcal, n=141	Wound healing	No significant difference in wound healing overall. Post-hoc analysis, patients with albumin </= 40g/L (n=127) had significantly greater total wound healing at 16 weeks with supplementation vs control (p=0.0325). In patients with baseline ankle-brachial index <1 (n=119) significantly greater total wound closure in supplemented group compared with control (p=0.0079), patients with low albumin had significantly greater proportion of total healing compared with control (p=0.0042). No significant difference in adverse events between groups

Table 4 continued. Combined Arg containing supplements with other active nutrients: characteristics of included primary studies

Author/ year	Methods	Setting	Patient characteristics	Age (years±SD)	Sample size	Treatment	Comparitor	Outcomes	Results
Bauer, 2013[52]	Pragmatic, randomised	Acute care inpatient/ outpatient setting, Australia	Chronic wound (venous ulcer, pressure ulcer, surgical wound)	67.8 (±22.3)	24	Open labelled wound ONS 2x 237mL/day (21g Ptn, 2100kJ, 9g Arg), n=12	Standard ONS, 2x/day (18g Ptn, 2100kJ), n=12	Wound healing (PUSH tool), nutritional status (patient-generated SGA), nutritional intake	Significant improvement in PUSH score in standard ONS group at 8 weeks (p=0.017) but not wound-ONS group. 3 patients fully healed in standard ONS group, 0 in wound ONS group. No significant difference in supplement compliance/ intake between groups
Kaya, 2016[53]	RCT	Thoracic surgery clinic, Turkey	Anatomic lung resection for non-small cell lung cancer	58 (±8.8)	58	Pre-op ONS support, immune modulating, Arg, omega-3 fatty acids, nucleotides for 10 days, n=31	Normal pre-operative diet, no additional ONS, n=27	Complication rates, drainage tube times (anastomotic healing surrogate)	Significantly less complications (p=0.049) and lower mean drainage tube times (p=0.019) in intervention group
Moya et al., 2016[54]	Prospective, randomised trial	Spain, University Hospital	Pre-op colorectal cancer diagnosis, for laparoscopic colorectal resection, normo-nourished	Intervention: 69 (51–85). Comparator: 68 (45–92)	128 (122 allocated)	Pre/peri-operative immune-enhancing dietary supplement: (IEF)-ATEMPERO, 7 days pre and 5 days postoperative. 2x 200mL cartons/ day (providing 604kcal, 33.2g ptn, 4g Arg, .8g RNA, 3.08g omega-3 fats, 8.8mg zinc, 676mcg Cu, 28.4mcg Selenium); n=61	Dietary advice only; n=61	Infections (wound), anastomotic leakage, abdominal abcess, LOS	No difference in LOS, significant decrease in wound infections (p=0.006), no difference in surgical complications
Moya et al., 2016[55]	RCT, multi-centre single-blinded	Colorectal cancer, Spain, 6 hospitals	Pre-operative colorectal cancer diagnosis, for colorectal surgery, normo-nourished	Median 69 (range 41–89)	244	Pre/peri-operative immune-enhancing dietary supplement: (IEF)-ATEMPERO, 7 days pre and 5 days postop. 2x 200mL cartons/ day (providing 604kcal, 33.2g ptn, 4g Arg, .8g RNA, 3.08g Omega-3 Fas, 8.8mg zinc, 676mcg Cu, 28.4mcg Selenium); n=122	Pre/peri-operative high ptn dietary supplement: (HHS)-SUPRESSI, 7 days pre and 5 days postop. 2x 200mL cartons/day (providing 500kcal, 25.2g ptn, 0g Arg, 0g RNA, 0g Omega-3 FAs, 5.6mg zinc, 564mcg Cu, 23.6mcg Selenium); n=122	Infections (overall including wound), anastomotic leakage, minor surgical site infection, major surgical site infection (abdominal abcess), LOS	No significant differences in ONS compliance between groups. No significant difference in LOS, Significantly less infectious complications in intervention group (p=0.007), significantly less minor and major surgical site infections in intervention group (p=0.005, p=0.008), no significant differences in anastomotic leak rates (p=0.301)

Table 4 continued. Combined Arg containing supplements with other active nutrients: characteristics of included primary studies

Author/ year	Methods	Setting	Patient characteristics	Age (years±SD)	Sample size	Treatment	Comparitor	Outcomes	Results
Falewee, 2014[56]	Multi-centre DBRCT	8 centres in France	Patients with upper aerodigestive tract cancer for surgical intervention	Intervention: 58.2 (±8.7). Comparator 1: 59 (±9.7). Comparator 2: 59.5 (±9.6)	298 randomised, 205 completed	Peri-op IN (Impact): 7 days pre-operatively orally, and 7–15 days postoperative EN Impact, n=73	1. Pre-operative IN (Impact): 7 days pre-operatively orally, and 7–15 days postoperative EN without immunonutrients, n=68. 2. No IN pre-and postoperative ONS/EN without immunonutrients n=64	Systemic infections, surgical site infections, LOS	No significant difference in infections, surgical site infections, LOS. When adjusted for compliance and at least 75% consumption of ONS/EN, significant difference seen between intervention and no IN group for decreased surgical site infections (p=0.04), and trend towards decreased systemic infections (p=0.05) and LOS (p=0.05). LOS significantly increased for patients who developed infectious complications (p=0.001)
Felekis, 2010[57]	DBRCT	Department of Otolaryngology, University Hospital, Greece. Recruited between 2004–2008	Patients with head and neck squamous cell carcinoma for surgical intervention	Intervention: 61 (±3.8). Comparator: 62.1 (±2.6)	40	5 days pre-operative IN (Impact) + diet to meet EER, postoperative EN with IN (Impact) for 8 days, n=20	No pre-operative nutrition support, oral diet to meet EER, postoperative standard EN (Nutrison, Nutricia) for 8 days, n=20	Postoperative complications	Significantly less major postoperative complications (systemic infections, fistula development) in intervention group (p<0.05)
Fujitani, 2012[58]	Multi-centre RCT	Japan, recruited between Feb 2006 – Dec 2009	Elective total gastrectomy patients due to gastric cancer	Intervention: 64 (26–76). Comparator: 65 (30–79)	244 randomised, 224 underwent gastrectomy and included in analysis	5 days pre-operative IN (Impact) (100mL/ day orally) + diet, n=127	Pre-operative diet only, n=117	Surgical & non-surgical complications, LOS	No significant difference between complication rates or LOS overall. When adjusted for weight loss >/< 5% body weight in 3/12 pre-operatively: significantly less surgical site infections in intervention group (p=0.031). Trend towards unfavourable outcomes for IN when BMI>25kg/m^2 (RR 2.86, CI (0.68, 12.12)
Klek, 2011[59]	DBRCT	Poland, General Surgery Department, University Hospital. Recruited Jan 2003 – Dec 2009	Malnourished patients undergoing gastrectomy and/or pancreato-duodenectomy for cancer resection	Ix: 60.2 (±12.4), Comparator: 61.5 (±11.8)	305 randomised	Standard PN 10 days pre-operatively then postoperative IN via jejunostomy (Reconvan: per 100mL; EPA + DHA=0.25g, Gln 10.2g, Arg 6.7g) for 7 days, n=152	Standard PN 10 days pre-operatively then postoperative standard EN via jejunostomy (Peptisorb: per 100mL- EPA + DHA=0g, Gln 0.35g, Arg 0.23g) for 7 days, n=153	Postoperative complications (infective & surgical, wound dehiscence, anastomotic leak, pancreatic fistula), LOS, mortality	Intervention group had significantly less infectious complications (p=0.04), decreased surgical wound infections (p=0.01077), decreased mortality (p=0.03), trend towards decrease wound dehiscence (p=0.05502), significant decrease in LOS (p=0.006)
Hamilton-Reeves, 2016[60]	DBRCT-pilot	Kansas, USA	Radical cystectomy for primary bladder cancer, men		29	IN (Impact Advanced recovery), 3x cartons/day for 5 days pre & 5 days postoperatively. n=14	Standard ONS (Boost Plus) 3x cartons/ day for 5 days pre & 5 days postoperatively. n=15	Postoperative complications & infections, LOS	IN group had 33% reduction in postoperative complications (p=0.06) & 39% decrease in postoperative infections (p=0.027) at 90 days. No diff in LOS

AOx = anti-oxidant; CHO = carbohydrate; EER = estimated energy requirements; HPE = high protein & energy; IN = immunonutrition; ONS - ON support; Ptn = protein; SGA = subjective global assessment

Mayes and colleagues[64] in their RCT administered *Lactobacillus rhamnosus GG* (15 billion CFU/dose), or placebo twice daily to their cohort of 20 paediatric acute burn patients requiring feeding tubes, until 95% wound closure was achieved. They reported trends towards lower requirements for operative excision/grafting procedures (p=0.23) and time to complete healing (p=0.23) with supplementation; however, no difference in medical LOS. It should be noted, however, that this small study was designed to evaluate the safety, not the efficacy, of supplementation with probiotics following burn injury and, as such, this study was underpowered to determine statistical effects on outcomes of interest to this review.

Bioflavenoids

Two studies were identified that Bioflavenoids alone[18] or combined with anti-oxidant nutrients[65]. In the study presented by Serra and colleagues[18] in 83 patients with venous leg ulcers for more than 6 weeks, 8 months' supplementation was shown to have an improved healing rate at 12 months (83.8%) compared to the comparator group (60.56%)[18]. In contrast, in the small cohort of 20 superficial to partial thickness adult burn injury patients reported by Raposio et al.[65], supplementation of bioflavonoids combined with anti-oxidants demonstrated no differences on LOS (p=0.63)[65].

Alternate nutritional intervention strategies

Five additional studies identified investigated alternate or novel strategies not categorisable to the groupings above[22,66–69]. Fifteen studies identified as part of the search strategy investigated heterogenous early EN, PN or ON support regimens in various medical conditions[63,70–83]. Characteristics of these studies are summarised in Table 5. Despite population groups, early EN and ON interventions appeared to have positive effects on outcomes of interest, especially when compared to PN interventions.

In the RCT presented by Najmi and colleagues[67], 100 patients with 10–20% second degree burns were provided an oral diet consisting of 20% protein, 60% carbohydrate and 20% lipid until discharge. The intervention group received their lipid from olive oil sources, whilst the control group received their lipid from sunflower oil[67]. The provision of lipid from olive oil was reported to significantly decrease the duration of wound healing (p=0.01) and LOS (p=0.05)[67]. The DBRCT, parallel group study by Babajafari and colleagues[69] investigated the effect of isolated soy protein supplementation with and without flaxseed oil as a functional food versus a wheat flour and corn oil food (cookie) comparator in 73 patients with 20–50% total body surface area (TBSA) burn injuries. Significant improvements were seen in wound healing in the isolated soy protein groups compared with the control at days 22 and 25 (p<0.05)[69]. All groups demonstrated a significant reduction in wound size from baseline over the 3-week study period (p<0.001); however, there was no significant difference between groups overall (p=0.7)[69].

An open label, parallel group study conducted by de Franciscis and colleagues[22] investigated the supplementation of folic acid (1.2mg/day) for 12 months in 87 patients with chronic venous ulcers who had hyperhomocysteinaemia (HHcy) versus chronic ulcer patients without HHcy and not supplemented with folate[22]. This study demonstrated a significantly higher rate of healing in the folic acid group than the comparator (p<0.05)[22].

The RCT conducted by Fujita and colleagues[68] investigating the rate of anastomotic leaks following thorascopic esophagectomy for cancer resection, provided their intervention group with a continuous, warmed intra venous infusion of 18 amino acids for 30 minutes prior to and during surgery[68]. They reported a significant decrease in surgical site infections (p=0.029) and no difference in anastomotic leaks (p=0.76) in their cohort of 130 participants[68].

A prospective, controlled, before and after comparative interventional study conducted by Bell and colleagues[66] investigated two differing nutritional care models on outcomes for 116 patients who had sustained hip fractures that required surgical intervention[66]. The treatment group received a multidisciplinary nutritional care model, whilst the comparator group received individualised nutrition care[66]. Whilst the intervention was shown to increase intake of energy (by 210%) and protein (by 207%), recruitment numbers were insufficient to determine an effect on pressure areas, surgical site infections, or mortality[66].

One additional systematic review was also identified that investigated nutrition strategies not elsewhere reported[84]. In the systematic review presented by Masters and colleagues[84], two studies with a total of 93 participants, published prior to the year 2000, were included[84]. One study investigated the use of two different high fat EN feed preparations versus an high carbohydrate EN feed[84]. The second study compared a high fat EN feed control group to two high carbohydrate EN feed groups, one supplemented with omega-3 fatty acids[84]. Due to the low participant numbers and heterogeneous nature of the included studies, no solid recommendations could be offered by the review authors regarding optimal fat to carbohydrate ratios in the EN feed provision to burn injury patients[84].

Discussion

Despite the recognised importance of nutrition in wound healing, this review has highlighted the paucity of high quality evidence generated in this field over the past decade and the difficulty in its interpretation. One major limitation with interpreting much of the literature in this field is the combined nutrient strategies. This prevents the active nutrients and optimal dosage from being deduced. Another limitation of these studies is the lack of nutritional intake or status (pre- and/or post-intervention) being reported or taken into consideration with the study design, such as in those reported by Serra et al.[18], Raposio et al.[65], and

Table 5. Early EN, PN and/or ON support strategies: characteristics of studies

Author/ year	Methods	Setting	Patient characteristics	Age (years)	Sample size	Treatment	Comparitor	Outcomes	Results
Vicic, 2013[70]	RCT	Burns Unit, Croatia	Burns >20% TBSA, >18 years old	20–76 (mean 48)	101	NJT feeds within 4 hours of admission, n=52	Standard diet, 3 meals/day, commenced immediately after the first wound dressing, n=50	Complications, wound infection, mortality	Sig less total complications (p=0.048), no sig diff in wound infections, sig lower mortality (p=0.03)
Barlow, 2011[71]	Multi-centre RCT	Regional United Kingdom Cancer Network	All adult patients admitted with suspected operable upper GI cancer. All patients had feeding jejunostomy inserted at time of operation	64 (57–72)	121	Early EN (EEN), commenced within 12 hours postoperatively at 20mL/hr, 1kcal/mL formula, increased by 10mL/hr every 12 hours until goal of 80mL/hr achieved. Pancreatic resections started at 10mL/hr, 1.3kcal/mL feed and increased 10mL/12 hours until goal. Once oral intake commenced, EN continued overnight 1.5kcal/mL feed over 12 hours until 75% nutritional requirements achieved orally. n=64	IV fluids until commenced oral fluids, diet started post contrast swallow if no anastomotic leaks, if anastomotic leaks EN/PN commenced at discretion of surgeon. Nutritional requirements calculated at 30kcal/kg/day. n=57	LOS, operative morbidity/ mortality. Complications: Wound infection, open abdominal wound dehiscence, anastomotic leak	Significantly lower median LOS with EEN (p=0.023), no difference in re-admissions (p=0.237). Less operative morbidity overall in EEN group (p=0.044). Significantly less wound infections (p=0.017), non significant decrease in anastomotic leaks (p=0.055). Wound dehiscence not reported
Khorasani, 2010[72]	RCT	Burns Unit, Iran, Sept 2002–2004	Children hospitalised with burns, 30 days – 12 years of age, burn ≥10% TBSA, sustained injury within 2 hours prior to admit	Intervention: 5 (±3.5). Comparator: 5 (±3)	688	EN commenced between 3–6 hours post burn. n=366	Conventional IV resuscitation in first 48 hours, then EN after 48 hours. n=322	LOS, mortality	Significantly lower LOS in intervention group (p<0.05), significantly lower mortality (p<0.05)
Li, 2015[73]	RCT	China	Head trauma patients requiring surgery	Intervention: 52.3 (±2.5). Comparator: 53.1 (±3.7)	120	EN, via NGT. Commenced 48 hours postoperatively, 45g of full nutrients (inc 2g Gln/100g) added to 170mL water (200mL total), 6–7 feeds/day n=60	PN, commenced 48 hours postoperatively, included “glucose, fat milk, multi amino acids, vitamins, and trace elements”. After 7–8 days EN commenced n=60	Complications, monitoring time	Total complications significantly lower in EN group (p<0.05) (pressure sores 2 vs 5, stress ulcers 1 vs 6), significantly shorter monitoring time (p<0.05)

Table 5 continued. Early EN, PN and/or ON support strategies: characteristics of studies

Author/ year	Methods	Setting	Patient characteristics	Age (years)	Sample size	Treatment	Comparitor	Outcomes	Results
Kim, 2015[74]	RCT	South Korea, Jan 2013 & Aug 2013	Living donor liver transplant	Intervention: 52 (43–65). Comparator: 52 (36–64)	36	EN, NGT placed several days postoperatively, feeding commenced within 12 hours of tube placement, commenced at 20mL/hr then if tolerated increased to 60mL/hr by day 5. Low residue feed. EN discontinued when patient could consume >50% of provided diet. n=17	Maintenance on IV fluids until oral diet commenced n=19	Infectious complications, LOS, nutritional status, mortality, complications	Significantly less infectious complications (p=0.043), no difference in nutritional status between groups, no mortality, significantly less bile duct complications (p=0.041)
Yadav, 2013[75]	Case Series, Historic Control	India, Intervention group Jan 2011 – Feb 2012, retrospective control group Jan 2010 – Jan 2011	Children under 12 undergoing elective ileostomy or colostomy closure	Intervention: 43.3 months (±38.5). Comparator: 38.2 (±41.4) months	62	Early EN protocol, full strength pasteurised milk, starting at 24 hours postoperatively, 1–2mL/kg every 2 hours and increased by 1mL/kg after every 2 feeds if tolerated, n=31	Feeds started once NGT removed after clinical onset of bowel activity and decrease in aspirates, varied from 3–5 days, progressed as tolerated. No standardised protocol, n=31	LOS, postoperative complications (wound dehiscence, anastomotic leak)	Significantly lower LOS in intervention group (p<0.0001), no significant difference in anastomotic leaks or wound dehiscence (p=0.31)
Pragatheeswarane, 2014[76]	RCT	India	Consecutive patients who underwent open bowel surgery	Intervention: 46.5 (±17.2). Comparator: 46.9 (±16.5)	120	Early feeding, oral fluids day 1 postoperatively, commencing at 24 hours, full fluid diet within 48 hours, solid diet in next 24 hours. n=60	Traditional feeding, nil by mouth until resolution of ileus, starting clear fluids progressing to solid diet as tolerated. n=60	Mean time to solid diet, LOS, Wound infection, anastomotic leak, mortality	Significantly shorter time to solid diet (p<0.0001), Significantly shorter LOS (p=0.019), no significant difference in wound infections, anastomotic leak, mortality
Amanollahi, 2013[77]	DBRCT	Iran, Feb 2011 and Sep 2012	Children 1 month – 12 years who underwent intestinal resection and anastomosis	Intervention: 17.4 (±24.6) months. Comparator: 23.7 (±32.6) months	67	Early feeding, clear fluids 24 hours postop, progressed to milk liquids then soft and normal diet next day (after 48 hours). n=37	Late feeding, fasted for 5 days, PN commenced postoperative day 2. n=30	LOS, major postoperative complications (wound infection, dehiscence, anastomosis leakage), intra-abdominal abscess	Significantly shorter LOS (p<0.0001), no significant difference in complications or anastomotic leak, no mortality,

Table 5 continued. Early EN, PN and/or ON support strategies: characteristics of studies

Author/ year	Methods	Setting	Patient characteristics	Age (years)	Sample size	Treatment	Comparitor	Outcomes	Results
Botella-Carretero, 2010[78]	RCT	Spain, May 2007 & Sep 2008	Normal or mildly undernourished geriatric patients admitted for hip fracture surgery	>65	60	ONS: 2x 200mL Fortimel/day providing 40g Ptn & 400kcal/day. From admission, maintained until discharge in addition to diet prescribed to meet EER. n=30	No ONS. Diet prescribed to meet EER only. n=30	LOS, postoperative complications, infections (wound), mortality	No mortality. No difference in LOS, infectious complications, weight. Intervention group had higher kJ (p=0.042) and Ptn intake (p<0.001). Higher Ptn intake was associated with lower postoperative complications (p=0.003)
Fabian, 2011[79]	RCT	Trauma centre, Austria	Female patients, >65 years old, with hip fracture	Intervention: 85 (±7). Comparator: 82 (±8)	23	Postoperative ONS (E, Ptn, Aox), administered individually when energy or Ptn intake did not exceed 20–15kcal/kg and/ or 1–1.5g/kg Ptn. Continued for duration of LOS. n=14	Standard postoperative nutrition. n=9	LOS	Average LOS shorter in ONS group (17±4 days) than controls (19±9 days)
Anbar, 2014[80]	RCT	Orthogeriatric unit, Israel. May 2010 to Dec 2011	Consecutive patients admitted within 48 hours of hip fracture injury, >65 years old, requiring surgery	Intervention: 82.3 (±6.1). Comparator: 83.7 (±6.4)	50	Tight calorie control, hospital diet + ONS (Ensure Plus). Pt, family, caregivers educate	Standard diet, providing a mean 1800kcal & 80g Ptn daily, fixed ONS prescription continued if commenced prior to admit	Postoperative complications, LOS	Significantly lower total complications in intervention group (p=0.012), non-significant trend towards shorter LOS (p=0.061), no significant difference in mortality. Significantly higher mean daily energy intake (p=0.001),significant negative correlation between cumulative energy balance and total complication rate (r=–0.417, p=0.003) as well as LOS (r=–0.282, p=0.049)

Table 5 continued. Early EN, PN and/or ON support strategies: characteristics of studies

Author/ year	Methods	Setting	Patient characteristics	Age (years)	Sample size	Treatment	Comparitor	Outcomes	Results
Roth, 2013[81]	RCT	Switzerland, Sep 2008 – Mar 2011	Consecutive bladder cancer patients undergoing cystectomy	Intervention: 67 (34–80). Comparator: 66 (30–86)	157	PN providing 1860kcal/day from postoperative day 1–6 + oral fluid from postoperative day 1, solid diet commenced on return of bowel sounds & fluids well tolerated n=74	IV fluids + oral fluid from postoperative day 1, solid diet commenced on return of bowel sounds & fluids well tolerated n=83	Infectious complications, postop mortality, LOS, wound dehiscence	Significant increase in postoperative complications (p=0.013), Significant increase in infectious complications (p=0.001), no difference in mortality, no difference in wound dehiscence, no difference in LOS (p=0.37)
Gao, 2018[82]	RCT	China, Jun 2007–2013	Admitted for sacretectomy	Intervention: 57.44 (±10.76). Comparator: 51.76 (±10.2)	48	Liquid diet (Nutrison Fibre) 25kCal/kg for 3 days pre-operatively, fasted with bowel preparation night before surgery. Postoperative PN, 25kCal/kg non-protein calories for 7 days until gradual re-introduction of oral diet. n=24	Liquid diet (Nutrison Fibre) 25kCal/kg for 3 days pre-operatively, fasted with bowel preparation night before surgery. EN, Nutrison Fibre, 25kcal/kg day 1–7 post surgery then gradual re-introduction of oral intake. n=23	Surgical site infections, healing time, LOS	Decreased healing time, surgical site infections, and LOS (p<0.05)
Chen, 2017[83]	RCT	China, Jan 2014 – Dec 2016	Confirmed gastric outlet obstruction with upper GI contrast and gastroscopy, age 18–80, surgically curable disease	Intervention: 52.1 (±13.2). Comparator: 48.6 (±12.5)	68	Total daily caloric intake 35kcal/day EN + top up PN to goal calorie target. 500mL feed day 1, increased be 500mL/day every 24 hours until target reached and maintained for 14 days pre-surgery. Post-op PN transitioned to EN as GI functioned recovered to meet 35kCal/kg. n=37	PN (all in one bag) caloric goal maintained for 7 days pre-op. Postop PN transitioned to EN as GI functioned recovered to meet 35kCal/kg. n=31	LOS, postop LOS , surgical site infections, anastomotic fistula, poor wound healing, mortality	Significantly improved wound healing (p=0.042), significantly decreased surgical site infections (0.046), no difference in anastomotic leak (p=0.136), longer LOS but shorter postop LOS (p=0.001)
Ohura, 2011[63]	Multi-centre RCT	Japan, medical institutions	Tube-fed patients with stage III–IV PI in sacral, coccygeal, trochanteric, calcaneal regions	58–95	60	Racol tube feed at Harris Benedict equation BEEx1.1x1.3–1.5. n=30	Racol tube feed at standard prescription (not stated). n=30	Healing (NPUAP classification and DESIGN tool)[46]. Nutritional parameters	Significant improvement in wound size (decrease) in intervention compared to comparator (p<0.001)

AOx = anti-oxidant; BEE = basal energy expenditure; EER = estimated energy requirements; GI = gastrointestinal; NGT = nasogastric tube; NJT = naso jejunal tube; ONS = ON support; Ptn = protein

Fujita et al.[68] amongst others reported in this review. This is of particular importance in determining the effect of a nutritional intervention on wound healing, especially given the difference seen in nutritional interventional effectiveness by many studies that have included nutritional status as part of their outcome analysis. Although one would assume than malnourished patients may have better wound healing outcomes than well-nourished patients, this effect was not observed in the study conducted by Leigh et al., where well-nourished patients showed a trend towards improved healing rates compared to malnourished participants when supplemented with Arg for non-healing PIs[46]. In addition to this complexity in literature interpretation, some studies explicitly measured and reported on compliance with ON supplementation and accounted for this in their statistical analysis or reporting[46–48,50,61], whilst other studies failed to report on compliance[53,55,60]. Such distinctions in nutritional status and compliance is important for clinicians to apply the correct nutrient prescriptions to their populations for optimal efficacy and fiscal justifications.

Another limitation in interpreting and comparing efficacy of nutritional intervention strategies reported in the current literature is the lack of standardisation in wound healing outcome measures used. For example, the fairly homogenous wound group of PIs, multiple tools such as the PUSH, overall percentage size, change in surface area, and time to healing were all reported for this outcome[46–48]. Whether effectiveness seen in chronic wounds is translatable to acute wounds, and vice versa, is also unknown.

Despite the limitation of this review only searching one database representing all Medline listed investigations, the majority of primary studies identified were single centre and small in sample size. This likely reflects the complexity in conducting high quality nutrition intervention research given the limitations of population type and numbers. One example of this issue is the comparatively large study conducted by Falewee et al.[56]. Despite having a strong study design including eight recruitment centres, their pre-determined sample size was not met due to inadequate recruitment in the allocated study timeframe[56]. The majority of studies identified were also conducted in adult populations, with only five identified being conducted in paediatric participants – three in burn injury, one in ileostomy/colostomy closure, one in intestinal resection[64,72,75,77,85]. This paucity in paediatric wound healing literature is of concern given the importance of adequate nutrition for optimal growth and development in this population[86]. This may be reflective of the small numbers of paediatric wounds presenting comparatively to the adult population or complexities in establishing or conducting research in this setting. This lack of specific evidence for the paediatric population potentially hampers the delivery of optimal nutrition support for wound healing in this setting.

Health professionals endeavour to base their recommendations on the available evidence, and guidelines aim to assist translation of evidence into practice[1]. This review identified that the more recent evidence for some of the key recognised macro and micronutrients involved in wound healing is, in many instances, weak, and often this is due to research design and reporting limitations. Encouraging further research in specific areas of deficiency, such as that identified in the paediatric population, is recommended. That being said, health professionals should always be recommending adequate amounts of highly nutritious food and fluids for general wellbeing in accordance with the guidelines for healthy eating[86]. When it comes to aiding wound healing in complex wounds, nutrition is an integral strategy to complement good wound hygiene practice and care[1].

Nutrition as an important consideration for best outcomes has been included in the care of complex burns for decades[87], so why is it not an automatic consideration in slow to heal wounds, chronic wounds, dehisced surgical wounds? It seems that because there is no specific evidence for each wound type and nutrient intervention, the nutrition aspect has often given less importance. Nevertheless, some of these studies provide sufficiently strong evidence to influence clinical practice. For example, arginine administered as a single interventional agent appears to convey some benefits for wound healing outcomes in the surgical oncology patient populations, at a higher administered doses (12–20g/day) for at least 10 days. Evidence in other populations remains insufficient to support its routine use. It also must be noted that there are recommendations for caution with its administration in the ICU setting. The Canadian Critical Care Guidelines, considering unpublished evidence showing possible increased mortality when initiated in severely septic medical ICU patients (however, not in patients who are already established on Arg who later become septic), make this recommendation[88].

The combination of arginine with other anti-oxidant or immune-modulating appears to offer benefit in malnourished patients with chronic wounds such as PIs, and has been shown to convey cost benefits to care[47,62]. The lack of effect seen in the systematic reviews identified as part of this search strategy are not surprising[39]. This area of research is diverse in its inclusion criteria, doses and nutrients administered, outcome measures and often of small scale. This is prohibitive to the accurate pooling of data to determine effects, as well as the ability to ascertain the key nutrients providing benefit. Regarding the management of chronic wounds, dosage of 4.5–9g/day administered orally appears effective. To strengthen this area of research, future studies should also employ cost benefit analysis to assist with determination of efficacy and translation of evidence into clinical practice for these types of nutritional strategies[10].

The administration of Gln via the EN route appears to convey a beneficial effect, particularly in burns and trauma patients, compared to PN administration[10,30]. This may be due to its

Table 6. Guideline macronutrient recommendations

	Trans Tasman Dietetic Wound Care Group[93]	NPUAP[1]	PEN[94]
	Moderate risk of delayed PI healing	PI, malnourished or risk of malnutrition	PI, risk of malnutrition
Energy	30–35kcal/kg/day	30–35kcal/kg/day	30–35kcal/kg/day
Protein	1.25–1.5g/kg/day	1.25–1.5g/kg/day	1.25–1.5g/kg/day
Fluid	30–35mL/kg/day	Individualised based on clinical condition, goals of care	Individualised based on co-morbidities/ goals, symptoms

role as a primary metabolite for gut enterocytes, improving gut integrity and preventing known sources of sepsis such as bacterial translocation of the intestinal tract[10]. To elucidate this effect it is important to calculate Gln dosages in addition to total protein requirements. Similarly to Arg it is sometimes administered as part of combined immune-nutrition regimens which complicates the ability to determine the most beneficial nutrient[29,59]. These regimens, however, have been proven to be safely administered in certain populations, and potentially may decrease time to healing and LOS[89–92]. The inclusion of the omega-3 fatty acids EPA and DHA likely improves the effect of these immune-nutrition regimes as they are metabolised to comparatively less inflammatory and less immunosuppressive metabolites than omega-6 fatty acids[10]. Dosage of supplementation appears to be more important with Gln than Arg, with ≥0.3g/kg/day via the EN route required to be effective[30]. Dosage studies have proved that up to 60g/day of Gln appears to be safe to administer. Importantly, the administration of Arg and Gln, for the purpose of improving wound healing, should be provided separately to the overall global protein required. If given as part of the general protein requirements or possibly where insufficient energy intake is consumed, they are utilised via different metabolic pathways negating their beneficial effects[30].

To elucidate the optimal implementation of research into clinical practice, multiple practice guidelines have been developed[1,31,93,94]. These guidelines all support the use of determining malnutrition risk using appropriate and validated screening tools as the first step of clinical management[1,93,94]. This should include weight status, weight history, and whether weight loss has occurred. Dietary adequacy of total nutrient intake should also be assessed, with guideline recommendations for macronutrients presented in Table 6[1,93,94]. As part of a comprehensive nutritional assessment, the risk of delayed wound healing due to nutritional compromise should be accounted for; as discussed previously, this is a limiting factor for many studies identified as part of this review. Although all the presented guidelines agree that the current levels of evidence for the use of combined nutritional supplements (containing high protein, Arg +/– Gln, omega-3 fatty acids and micronutrients) remains low, their use is supported in surgical populations[31,88] and for patients with greater than stage II or multiple pressure ulcers where nutritional requirements cannot be met with traditional ON support[1,93,94]. Findings from this review do not support changes to the current guidelines supporting nutrition and its role in wound healing reported in Table 6 and elsewhere in this discussion. Whilst not an exhaustive list of available guidelines, they are supported by peak nutrition and wound healing groups[1,31,87,88,93,94]. To ensure optimal wound healing in a clinical setting, following practice guidelines designed for relevant populations is a simple way to translate available evidence into the clinical setting until further large-scale, multi-centre, prospective nutrition intervention studies, including cost effectiveness outcomes, are available.

Conclusion

Nutrition is an integral component of best practice wound care. Despite the diversity of identified research over the past decade in this area, multiple nutritional strategies for various wound types are evolving. Current available guidelines provide broad consistency regarding macronutrient recommendations; however, evidence for other nutrient recommendations remains lacking, especially relating to optimal timing and dosage. Given the low cost in delivery of nutrition interventions compared to other complementary wound management strategies, such as surgical intervention and specialised wound dressings, this area warrants greater attention. Early nutrition screening and appropriate nutritional intervention for all wound types should be routine clinical practice.

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