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REVIEW ARTICLE

Role of nutritional supplementation in elderly patients with hip fractures

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Abstract Due to the ageing population there is an increasing incidence of hip fractures in the elderly. Oral nutritional supplements are being widely used to improve clinical outcomes and mortality post-hip fractures. The aim of this study was to review the available literature on the effects of oral nutritional supplements on elderly patients with hip fractures. A search of EMBASE (1988—present) and MEDLINE (1946—present) with the search terms: "nutritional supplement" AND "hip fracture"; "nutritional supplement" AND "femoral neck fracture"; "nutritional supplement" AND "intertrochanteric fracture"; "nutritional supplement" AND "subcapital fracture"; "hip fracture" AND "vitamin supplement"; "hip fracture" AND "protein supplement"; "hip fracture" AND "nutrient supplement" was carried out. Additionally, the reference lists of articles were searched for relevant areas of study. Few studies showed that oral nutritional supplementation led to a more positive clinical outcome amongst elderly patients suffering hip fractures. Most studies found little or nil positive results. Thus, the role of oral nutritional supplementation on post-hip fracture mortality, infection/complication rates, and hospitalisation/rehabilitation time amongst elderly patients is unclear. There is a need for a broader, randomised, placebo-controlled clinical trial on the effect of oral nutritional supplements and particularly on the supplements used commonly.

Introduction

With the ageing population expected to reach 25% of the total Australian population in 2056, there is an increasing demand on hospital services [1]. The incidence of hip fractures is also increasing, with one study projecting an increase by 15% every 5 years until 2036, and by 10% every 5 years after that until 2051 [2]. Morbidity and mortality

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following hip fractures are high, with mortality rates of 24% being seen within the 1st year post-fracture. Protein energy malnutrition is seen more often in patients suffering from hip fractures than their age-matched control comparisons [3]. Theoretically, by providing the malnourished elderly patient with nutritional supplements, it is supposed that their clinical outcomes may be improved.

The benefit of oral nutritional supplements (ONSs) in this clinical scenario has been a topic of debate. Many trials have found that ONSs indeed reduce hospital length [4], pressure ulcers [5], economic cost [4], mortality [6,7], and rates of infections or complications [6,8—10]. Postoperative complications are described as a wide range of individual conditions including wound infections, other infections [e.g., pneumonia, urinary tract infection (UTI)], deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, bedsores, delirium, severe anaemia, gastrointestinal (GI) ulcer, and cardiac failure. Others have found little or no benefit of oral supplements [11,12]. Despite their somewhat unclear benefit, a large variety of ONSs are available on the market.

The aim of this review is to analyse the available literature on the effects of nutritional supplements on the clinical outcomes (including mortality) of elderly patients suffering from a hip fracture.

Methods

A search of EMBASE (1988—present) and MEDLINE (1946—present) with the search terms: "nutritional supplement" AND "hip fracture"; "nutritional supplement" AND "femoral neck fracture"; "nutritional supplement" AND "intertrochanteric fracture"; "nutritional supplement" AND "subcapital fracture"; "hip fracture" AND "vitamin supplement"; "hip fracture" AND "protein supplement"; "hip fracture" AND "nutrient supplement" was carried out. Additionally, reference lists of articles were searched for relevant areas of study. The exclusion criterion included studies that did not use nutritional supplements, studies that did not focus on hip fractures, and studies that did not examine complications/outcomes that were affected by the use of nutritional supplements. The inclusion criterion was studies that focused on the effect of nutritional supplements on the clinical outcome of patients with hip fractures. The searches resulted in 94 EMBASE and 92 MEDLINE results. The authors manually sorted through the available literature to identify 12 studies that fit the inclusion criteria.

Results

Study participant profiles

All studies had set inclusion and exclusion criteria to determine the eligibility of the patient to participate in the identified study. Patient age varied from >60 years [13—17], >65 years [18], and >70 years [19]. Fabian et al. [20] included female patients >65 years and Sullivan et al. [21] included all patients >64 years, whereas Bastow et al. [3] included all "elderly" female patients with ages ranging from 68 years to 92 years. Most studies had time constraints in which the patient had to receive the surgical invention by, ranging from within 48 h [14,19], within 3 days [21], up to within 2 weeks [17], 3 weeks [16], and 4 weeks [15]. Exclusion criteria were very strict within all studies with pathological fractures [13—17,19—21,23,24], organ failure or severe trauma to multiple organs [3,13,16,18—21,23,24], mental incapacity (including dementia) [3,13—15,17,19] and contraindication to ONSs [13—15,18—21,23,24] being the most consistent exclusion criteria. Other exclusion criteria included concurrent malignancy [14,15,21,23], body mass index >25 [15], 30 [16], and 40 [23] as well as patients that were in an unstable condition [15,16], being treated with phenytoin, steroids, barbiturates, fluoride, or calcitonin [13], unable to be contacted by telephone for follow-up [16] or in need of dialysis [23]. Eneroth et al. [14] also excluded patients who had pain or functional impairment, alcohol or substance abuse, or multiple fractures as well as patients with acute psychosis or epilepsy. Botella-Carretero et al. [18] excluded patients with moderate to severe malnutrition (weight loss of >5% in the previous month or >10% in the previous 6 months, and/or serum albumin <27 g/L) because these patients automatically received supplementation according to the guidelines of their institution. Pregnant patients were excluded from Houwing et al.'s [23] study. Lastly, Schürch et al. [17] excluded those with a history of contralateral hip fracture, fractures caused by severe trauma, and patients with active metabolic bone disease, severe malnutrition, taking drugs such as calcitonin, fluoride, sex hormones, corticosteroids, or bisphosphonates, or had a life expectancy of <1 year. These exclusion criteria have clear reasoning behind them; however, studies may have excluded patients who would benefit from ONSs. Although including dementia patients poses an ethical dilemma, research has shown that they are more likely to be malnourished and thus may benefit more from such an intervention [25].

Nature of intervention

All studies compared an ONS group (the intervention group) to a control group. Most studies used hospital food as the control group [3,13—15,18,20,21,24]; however, Neumann et al. [16] compared a high protein ONS (Boost HP, Mead Johnson, Evansville, IN, USA) to the "control" group, Ensure (Ross Laboratories, Columbus, OH, USA) [16], and Espaulella et al. [19] compared an ONS, which provided 149 cal including 20 g of protein to a "control" group, an ONS containing 155 cal mainly derived from carbohydrates. Although this provided better blinding and the consequential "placebo effect", it can be argued that this was why both papers lacked significant results as caloric intake by both patient groups was increased, suggesting that increased protein intake may not necessarily improve clinical outcomes. Botella-Carretero et al. [18] compared two types of ONSs, the first a protein supplement (Vegenat-med Proteina, Vegenat SA, Badajoz, Spain) and the second an energy and protein supplement (Resource, Hiperproteico, Novartis Medical Nutrition, Barcelona, Spain) versus a control. Lastly, Houwing et al. [23] compared an intervention group to a control group that received a noncaloric-

based drink containing only sweeteners, colourants, and flavourings, thus providing a placebo and consequential blinding of the participants.

Types of nutritional supplements

Oral nutritional supplements vary greatly with different amounts of energy, carbohydrates, proteins, and fats. There was little consistency between the types of supplements used in the studies (see Table 1). The amount of fat per 100 mL varied from 0 g to 4 g, whereas the carbohydrate content per 100 mL varied more from 7.5 g to 22.8 g. Protein content also ranged considerably from 2.8 g to 10 g per 100 mL.

High protein versus low protein

Only one study, Neumann et al. [16], specifically investigated whether or not an ONS with increased protein levels would be more beneficial than one without such an increase. Espaulella et al. [19] did this incidentally by providing the control group with a placebo ONS containing no protein. Neumann et al.'s [16] study lacked any significant results, whether this is due to an insufficient increase in protein levels in the high protein ONS or whether increased caloric intake as provided by ONSs increases positive clinical outcomes regardless of formulation remains to be seen. Espaulella et al. [19] only had one significant result, that is, there was a decrease in the number of complications in the intervention group compared to the control group. However, the study that had the highest level of protein, 10 g in Eneroth et al.'s [14] ONS, had very significant results when comparing the ONS and hospital food to just hospital food finding that the ONS reduced the risk of fracture-related complications and reduced mortality rates.

High caloric versus low caloric

Botella-Carretero et al. [18] compared two different ONSs: the first provided 36 g of protein but only 152 kcal/day, whereas the second provided 37.6 g of protein and 500 kcal/day. However, significant results were only produced using multivariate analysis; there were no other significant results between any of the three groups. Although it is suggested that increasing protein intake is more important than increasing caloric intake (as other studies have implied), further research needs to be carried out on both increases in caloric and protein intake. Furthermore, it may be possible that caloric intake needs to be increased by more than 500 kcal to produce significant results.

Route

The route through which the supplement was administered differed between studies. In most studies it was given orally; however, Eneroth et al. [14] used an intravenous (i.v.) supplement for the 3 days following surgery as pain limited the use of an oral supplement after which an oral supplement was given for 7 days. Bastow et al. [3] used nasogastric feeding using Clinifeed Iso (Roussel Laboratories Ltd, Wembley Park, UK) overnight and Sullivan et al. [21] also used nightly enteral feedings. Gunnarsson et al. [24] used a glucose i.v. infusion preoperatively, whereas an oral supplement was used for 5 days postoperatively.

Timing

No study specifically investigated the effect of the timing of ONSs. It stands to reason that providing ONSs at the same time as normal hospital food will result in a reduction of voluntary food intake simply due to fullness. Bastow et al. [3], however, did note that although there was a small decrease in voluntary intake of food in patients receiving enteral nightly feeding it was not significant, and Delmi et al. [13] provided the ONS at 8:00 PM so as not to interfere with scheduled meals and thus it was found that the voluntary oral intake was not reduced in the intervention group. Other studies found similar findings and thus it can be concluded that overnight feedings will not impede on daily intake of food [26,27]. However, no other study investigated whether the timing of ONSs affected the normal eating habits of patients. More studies are required to determine whether it is more beneficial to provide an ONS overnight or during the day, prior to or after normal meals, or between meals. Similarly, different servings of ONSs provide different nutritional supplements, yet no study investigated whether an increase in ONSs would increase benefits in clinical outcomes or whether the increase would further suppress normal caloric intake.

Data analysis

Data analysis was consistent across all studies with nine using the Student (unpaired) *t* test [3,13,15,16,19–21,23,24] and seven using the χ^2 test [13–15,18,19,21,24]. The Mann–Whitney *U* test was used by eight studies [3,13–15,18,19,23,24], whereas Eneroth et al. [14], Fabian et al. [20], and Gunnarsson et al. [24] used the paired *t* test. Other tests used included the Kruskal–Wallis test by Myint et al. [15] and Botella-Carretero et al. [18], the Kaplan–Meier survival test and the log rank test by Espaulella et al. [19] as well as the Pearson linear correlation by Fabian et al. [20], and the van Elteren test by Neumann et al. [16]. Gunnarsson et al. [24] used the Wilcoxon signed rank test, whereas Botella-Carretero et al. [18] and Houwing et al. [23] used the Kolmogorov–Smirnov statistical test. Botella-Carretero et al. [18] also used analysis of variance, the Tukey HSD test, and a linear regression model. One-way analysis of variance was used in Schürch et al.'s [17] study. Lastly, the Fisher exact test was used in five studies [3,13,18,21,23]. These tests were each considered appropriate to the design of the study with consequential results deemed acceptable by the respective authors.

Serum albumin levels

Serum albumin levels were used by most studies as a method of measuring biochemical changes caused by the ONS. Myint et al. [15] found that those in the intervention group had a greater increase in albumin levels between

Table 1 Comparison of oral nutritional supplements (ONSs).

ONSs	Used by	Serving	Energy	Protein (per 100 mL)	Carbohydrate (per 100 mL)	Fat (per 100 mL)
Vitrimix	Eneroth et al. [14]	1000 mL	100 kcal/100 mL	5.3 g	7.5 g (glucose)	0.3 g
Fortimel	Eneroth et al. [14]	200 mL twice daily	100 kcal/100 mL	10 g	10.3 g	2.1 g
Ensure Abbott Nutrition, Columbus, OH, USA	Myint et al. [15]	237 mL twice daily	250 kcal/237 mL	3.7 g	16.9 g	2.6 g
Resource Breeze	Myint et al. [15]	237 mL twice daily	250 kcal/237 mL	3.8 g	22.8 g	0 g
Compleat	Myint et al. [15]	250 mL twice daily	106 kcal/100 mL	4.8 g	13.2 g	4 g
Glucerna	Myint et al. [15]	237 mL twice daily	200 kcal/237 mL	4.2 g	11.4 g	3.0 g
Ensure	Neumann et al. [16]	237 mL twice daily	250 kcal/237 mL	3.7 g	16.9 g	2.6 g
Boost HP	Neumann et al. [16]	250 mL twice daily	240 kcal/250 mL	6 g	13.2 g	2.4 g
ONS	Espaulella et al. [19]	200 mL daily	149 kcal/200 mL	10 g	n/a	n/a
ONS	Fabian et al. [20]	n/a	1000 kcal/1000 mL	Providing 40 cal/100 mL	Providing 41 cal/100 mL	Providing 19 cal/100 mL
ONS	Delmi et al. [13]	250 mL	254 kcal/250 mL	8.2 g	11.8 g	2.3 g
Clinifeed Iso	Bastow et al. [3]	1000 mL	1000 kcal/1000 mL	2.8 g	n/a	n/a
Promote	Sullivan et al. [21]	1375 mL	1031 kcal/1375 mL	6.24 g	13 g	2.6 g
ONS	Gunnarsson et al. [24]	Two drinks and i.v. infusion preoperatively	100 kcal/200 mL and 50 mg glucose/mL			
ONS	Gunnarsson et al. [24]	200 mL three times daily	300 kcal/200 mL	n/a	n/a	n/a
Vegenat-med Proteina	Botella-Carretero et al. [18]	10 g packets four times daily	380 kcal/100 g	9 g	$<$0.02	0.2 g
Resource Hiperproteico	Botella-Carretero et al. [18]	200 mL twice daily	250 kcal/200 mL	9.4 g	n/a	n/a
Meritene	Schürch et al. [17]	65 g powder supplement per day	250 kcal/serve	20 g/serve	35.7 g/serve	3.1 g/serve
Cubitan	Houwing et al. [23]	400 mL daily	125 kcal/100 mL	10.0	n/a	n/a

admission and 4-weeks post-discharge; however, this did not reach significance (6.0 g/L vs. 5.0 g/L). Levels of serum albumin were significantly greater in the intervention group when compared with the control group at Day 14, Day 21, and Day 180 ($p < 0.05$) in Delmi et al.'s [13] study. Fabian et al. [20] found that the total protein was significantly greater in the supplemented group when compared with the control group at discharge (69 ± 4 g/L vs. 64 ± 4 g/L, $p < 0.05$); however, albumin was not significantly greater in the supplemented group when compared with the control group despite some increase. Neumann et al. [16] found a greater improvement in serum albumin levels in patients on the high protein ONS (Boost HP) compared with the standard supplement Ensure ((+7 g/L) vs. (+2 g/L), $p < 0.02$). Espaulella et al. [19] found no significant difference in albumin levels between the control group and the intervention group (36 ± 6.0 g/L vs. 35 ± 5.0 g/L). Similarly, Sullivan et al., Eneroth et al. [14], Bastow et al. [3], Gunnarsson et al. [24], and Schürch et al. [17] found no significant difference in serum albumin levels between the two groups. Gunnarsson et al. [24] also investigated the effect on serum transthyretin and serum insulin-like growth factor 1 (IGF-1). There were no significant differences in serum transthyretin between groups; however, they found that although serum IGF-1 decreased significantly ($p < 0.001$) in the control group preoperatively to postoperatively, there was no significant difference in the intervention group, suggesting that low protein and energy intake results in low serum IGF-1. Botella-Carretero et al. [18] found no significant differences in serum albumin, serum prealbumin or retinol-binding globulin between groups. However, by using multivariate analysis, they were able to show that the length of hospital stay with an established complication until its resolution, total hospital stay, baseline body mass index, and total daily ingested proteins per body weight were predictive variables with regard to the change in serum albumin ($p < 0.001$). Houwing et al. [23] did not investigate the effects of ONSs on serum albumin levels.

Bone mineral density and IGF-1

Only the study by Schürch et al. [17] investigated the effect of ONS on bone mineral density (BMD). It was found that there was no significant difference in total body BMD between the intervention group and the control group. Schürch et al. [17] also examined prealbumin levels and IGF-1 levels and found that these levels increased significantly in those who received the protein supplement when compared with the control group. Furthermore, they found that the protein supplement was associated with an almost 50% reduction of proximal femur bone loss at 1 year. A significant increase in *immunoglobulin M* was also noted in the intervention group compared with the control group. These findings suggest that protein supplement may have an effect on immunological status.

Infections

Infections were poorly defined in studies that investigated the effect of supplementation on infections. Rather, in each study infections were classified differently with some studies focussing on specific infections, and others grouping all infections together and some considering infections as "complications" (see below). Eneroth et al. [14] found that the incidence of pneumonia was significantly greater in the control group at 10 days postoperatively (5 vs. 0, $p < 0.05$) and again at 30 days postoperatively (7 vs. 0, $p < 0.01$). Patients in the control group had a significantly higher number of wound infections within 30 days compared with those in the intervention group (12 vs. 2, $p < 0.01$). The number of UTIs was significantly greater in the control group at 120 days postoperatively (15 vs. 3 $p < 0.01$) but not at any stage prior to then. Myint et al. [15] determined that the number of infection episodes was significantly reduced in the intervention group (14 vs. 29 in the control group, $p < 0.02$); however, there were no significant differences in individual infections nor were "infections" precisely defined. Conversely, Neumann et al. [16], Fabian et al. [20], Bastow et al. [3], Sullivan et al., Schürch et al. [17], and Houwing et al. [23] did not investigate the effect of ONSs on infections. Four studies did not estimate the effect of ONSs on infections, rather they collated complications, including infections such as UTIs, with three finding significantly lower rates in the intervention groups [13,19,24]. The fourth study by Botella-Carretero et al. [18] found no significant difference in infections.

Complications

A number of studies focused on whether or not ONSs reduced the number of complications in patients. Each study defined complications differently with some including infections as well as other major complications, including death, and minor medical events. Espaulella et al. [19] found that patients in the control group suffered more complications during hospitalisation (45% vs. 31%, NS) and over the 6-month follow-up period (70% vs. 55%, $p < 0.05$) when compared with those in the intervention group. The most common complications were delirium, UTIs, and bedsores. Delmi et al. [13] determined that rates of complications (including bedsores, severe anaemia, cardiac failure, infection, GI ulcer) were significantly lower in the intervention group than the control group (16% vs. 37%, $p < 0.05$). Gunnarsson et al. [24] determined that females in the control group had significantly more postoperative complications (pressure ulcers and/or hospital-acquired infections) than females in the intervention group ($n = 18$ vs. $n = 10$, $p < 0.05$); however, as the male participants who made up 30% of the groups were not included in this statistic, it is suggested that this was not significant overall. Eneroth et al. [14] measured complications including thrombophlebitis, DVT, PE, pulmonary oedema, and myocardial infarction at Day 3, Day 10, discharge, Day 30, and Day 120. It was found that at Day 120, the control group had more complications than the intervention group; however, this was not significant (5 vs. 1, NS). Myint et al. [15] also found no significant results regarding complication episodes despite the control group having twice as many episodes (60 vs. 30, $p = 0.068$). In this study, complications included pressure sores, urinary retention, DVT, PE, anaemia requiring transfusion or iron supplements, falls, and electrolyte disturbances. Houwing et al. [23]

determined that although the incidence of peptic ulcers was not significantly affected by an ONS, it was found that it delayed the onset and progression of such a complication in hip fracture patients; however, this did not reach statistical significance. Neumann et al. [16], Sullivan et al., and Botella-Carretero et al. [18] found no difference between the groups with regard to complications and Fabian et al. [20], Bastow et al. [3], and Schürch et al. [17] did not evaluate whether the intervention reduced complication rates.

Length of stay

Length of hospital stay and/or rehabilitation stay is a rather good indication of a patient's recovery speed — the earlier they leave hospital, the faster they recover. A number of studies [3,13–16,20] investigated the effect of ONSs on hospital/rehabilitation stay, but it was questioned by Myint et al. [15] whether the reduction in stay was simply secondary to a reduction in infection episodes.

Myint et al. [15] found that rehabilitation stay was significantly reduced in the intervention group when compared to the control group (mean = 26.2 days vs. 29.9 days, $p < 0.05$). Neumann et al. [16] found that although the length of the rehabilitation stay was shorter in the Boost group (intervention group) it did not reach statistical significance (mean = 23.2 days vs. 28.0, $p = 0.27$). Fabien et al. [20] found that the average length of hospitalisation in the intervention group was 2 days shorter than in the control group (17 ± 4 days vs. 19 ± 9 days). They also determined that the length of hospital stay was positively correlated with increased levels of oxidative stress but negatively associated with albumin and total antioxidant capacity (the ONS was found to decrease levels of oxidative stress and increase levels of albumin and total antioxidant capacity). Length of hospital stay was also found to be significantly shorter in the intervention group when compared to the control group (24 days vs. 40 days, $p < 0.02$) in Delmi et al.'s [13] study. Bastow et al. [3] found that those in the tube fed group had a shorter hospital stay than those who were in the control group (median hospital stay of 29 days vs. 38 days, $p = 0.04$). Shorter rehabilitation stays were found to be significantly shorter in the intervention group when compared with the control (42.2 ± 6.6 days vs. 53.0 ± 4.6 days, $p < 0.02$) in Schürch et al.'s [17] study; however, it was also found that there was no significant difference in the length of hospital stays. Eneroth et al. [14] found no difference between lengths of hospital stay between groups with 12.5 days being the mean for both, whereas discharge rates were not significantly different in Sullivan et al.'s study. Hospital stays were similar in all three groups in Botella-Carretero et al.'s [18] study. Espaulella et al. [19], Gunnarsson et al. [24], and Houwing et al. [23] did not investigate the effect of ONSs on length of hospital stay.

Clinical outcome

Only two studies investigated the effect of ONSs on clinical outcomes of patients, the remainder did not specifically evaluate whether clinical outcomes could be improved through the use of ONSs. It was found that the clinical outcome in the intervention group in Delmi et al.'s [13] study was much better during their hospital stay with 56% having a positive course (i.e., had one "minor" complication, e.g., lower UTI or none) compared with 13% of the control group. Neumann et al. [16] found no statistically significant improvement in clinical outcomes using the Functional Independence Measure between the two types of ONSs, a standard supplement and a high protein supplement; whether an improvement would have occurred compared with hospital food is unknown.

Mortality

Seven of the 12 studies investigated the effect of ONSs on mortality rates [3,13–15,17,19,21]. However, only three of these found significant results [13,14,20]. Four patients (10%) in the Eneroth et al.'s [14] control group died, whereas there were no deaths in the intervention group ($p < 0.04$). One death was from general weakness and malnourishment, whereas the other three were due to pneumonia. This leads to the question whether it was the reduction in complications (i.e., pneumonia), which was also significant in this study, that caused the reduction in mortality or whether there is a direct link between the use of ONSs and mortality. Delmi et al. [13] found that patients in the control group had a significantly higher mortality rate (37%) when compared with those in the intervention group (24%). In Sullivan et al.'s first feasibility study it was found that the mortality rate in the control group (50%, $n = 5$ out of 10) significantly far exceeded the rate in the intervention group (0%) [21]. However, in the follow-up study conducted 6 years later, no significance was found between mortality rates [22]. Myint et al. [15], Espaulella et al. [19], Bastow et al. [3], and Schürch et al. [17] all found similar mortality rates between the two groups. This even divide indicates that the effect of ONSs is still unknown and further research needs to be undertaken and possibly investigate the effect of different types of ONSs including high protein on mortality.

Malnutrition and infection

Studies have investigated the effect of malnutrition on the body's ability to combat infections. Keenan et al. [28] found that protein calorie malnutrition and deficiency in fatty acids, vitamins, and trace elements impaired cytokine production. Cytokines are soluble factors necessary for the communication between different cells required for an immune response. Some cytokines [e.g., interleukin 1 (IL-1) and tumour necrosis factor] are preformed but most require transcription of cytokine genes and subsequent translation of mRNA into protein to be formed. Furthermore, they found that patients who were receiving inadequate levels of proteins and calories had a reduced ability to synthesise IL-1α, which is necessary for inducing the synthesis of acute phase proteins. It was found that the ability to produce IL-1 correlates with dietary protein intake and was also associated with improved survival [28]. Munoz et al. [29] determined that IL-1β levels, which were low in malnutrition patients, increased significantly after 4 months of

nutritional rehabilitation. Low IL-1 activity was consequently able to explain the impaired ability for malnourished patients to mount a febrile response to infectious agents, which increases their risk for mortality [29].

In animal experiments, protein depletion caused an inability for rabbits to mount a febrile response to Gram-negative infections [30], whereas peritoneal macrophages from protein-depleted guinea pigs were unable to produce IL-1 [31]. Individual amino acids were found to have a direct influence on the immune system. Glutamine stimulates growth hormone, which directly and indirectly increases function of the immune system. Normally able to be synthetized by the body during stress, the body's demand for it exceeds its ability to create it, thus as a now essential nutrient, it is necessary for the catabolic process to produce optimal tissue response to infection as well as inflammation and catabolism. Glutamine was also found to increase neutrophils ability to kill *Staphylococcus aureus* [32]. Arginine, an essential amino acid, has been found to minimise negative nitrogen balance, stimulate the immune system, and improve wound healing. The latter is enabled as arginine stimulates growth hormone, glucagon, prolactin, and insulin [33].

It is not just a lack of macronutrients that have been implicated in increased infection susceptibility. Vitamin E is the most effective chain breaking, lipid-soluble antioxidant in biological membranes of all cells. Because of their high polyunsaturated fatty acid content, immune cells are at high risk for oxidative damage, thus they are enriched with large amounts of Vitamin E. Lack of vitamin E consequently incurs damage. Thus, vitamin E supplementation has found to improve immune function in the elderly and increase cell division and IL-producing capabilities of naïve T cells. This has been associated with significant improvement in resistance to influenza virus infection in aged mice and a reduced risk of acquiring upper respiratory tract infections in nursing home residents. There are several possible mechanisms as to why vitamin E is able to stimulate the immune system. One possible mechanism is the ability of vitamin E to enhance T cell mediated function by directly influencing membrane integrity and signal transduction in T cells. Another is by indirectly reducing the production of suppressive factors, such as prostaglandin E2 (PGE2), by macrophages. PGE2 is upregulated in the elderly, thus leading to the suppression of T cell immunity, by using supplements, vitamin E is able to prevent this suppression thus increasing the patient's ability to combat infections [34]. Another important micronutrient is zinc. Zinc deficiency has been found to reduce nonspecific immunity, including neutrophil and natural killer cell function and complement activity. It also reduces the numbers of T lymphocytes and B lymphocytes and suppresses delayed hypersensitivity, cytotoxic activity, and antibody production. Low zinc has also been found specifically in patients with pneumonia [35]. These studies, although suggesting the importance of specific macronutrients and micronutrients in fighting infections, have yet to be applied to human participants and specifically patients who have suffered from a hip fracture. By providing ONSs aiming to fill deficiencies of these nutrients, it is proposed that the patient's ability to combat infections will be increased.

Malnutrition and fracture healing

Animal studies have demonstrated the adverse effects of malnutrition and vitamin(s) deficiency on fracture healing. However, there is little information on whether these results correspond to human participants and whether the correction of such deficiencies will improve clinical outcomes. Pollak et al. [36] investigated the effect of different nutritional regimens on fracture healing in rats. It was determined that those who received low protein levels (5% of diet) resulted in significantly lower tensile strength and stiffness of calluses despite adequate caloric intake when compared with three other diets all consisting of greater levels of protein. Furthermore, this low protein diet resulted in a callus with "rubbery" mechanical properties rather than the "rigid" calluses of the other groups. Hughes et al. [37] also found that rats on a 30% protein diet had increased levels of albumin and BMD in the fracture callus when compared with rats on a 6% protein diet. However, there were no significant differences in biomechanical testing of the fracture. Finally, Guarniero et al. [38] determined that rats subjected to protein malnutrition prior to and after a fracture had abnormal callus development, and Rodrigues et al. [39] found that undernutrition produced a delay in callus formation in rats. Dwyer et al. [40] attempted to correlate the nutritional status of patients and the union of open fractures; however, they found no significant results relating malnutrition to bone union.

Malnutrition and sarcopenia

The relation of malnutrition to sarcopenia with consequential frailty in elderly patients has been established [41,42]. Furthermore, decreased lower extremity strength has been found to be a risk factor for injurious falls in the year after suffering a hip fracture, whereas malnutrition was found to be a risk factor for recurrent falls resulting in fracture [43]. However, the effects of ONSs and whether they are capable in reversing sarcopenia, especially in elderly hip fracture patients, has yet to be researched.

Discussion

Despite the elderly population expected to increase considerably, there is limited research evaluating the role of ONSs on hip fractures and ways to reduce complications, expensive hospital stays and, most importantly, mortality. The research that has been completed shows mixed results, with some finding entirely significant results and others finding no significant results. Furthermore, the majority of articles excluded important patients — those who suffered from dementia and/or were mentally incompetent to participate in the research. Although this does pose an ethical issue, it also precludes patients that are more likely to be suffering from malnutrition and thus in greater need of nutritional supplements [25].

Another issue found in the inclusion of all appropriate candidates was that of time, money, and protocol. Sullivan et al. were only able to enter patients from Monday to Friday, whereas Bastow et al. [3] were only able to include six patients at any one time, thus reducing the likelihood of

all patients who met the inclusion criteria being included in the study. Such constraints due to time and hospital protocol and staffing cause a reduction in numbers that could have increased the significance of the results. Lastly, Botella-Carretero et al. [18] were unable to include malnourished patients in their trial because of hospital protocol stating that all malnourished patients must receive nutritional supplementation. Consequently, from their mostly nonsignificant results, it can be concluded that ONSs do not have the same effect on nourished patients as they would on malnourished patients.

Lastly, although there has been much research on the effects of specific vitamins and minerals on immunity and reducing infections, it has yet to be applied to specific cases such as hip fractures. Furthermore, it can be surmised that the detrimental effects of malnutrition on fracture healing has well been demonstrated in animal participants; however, further research is necessary to make the connection between malnutrition and clinical outcomes in human participants and specifically those with hip fractures. Finally, it is yet to be determined whether ONSs are able to reverse sarcopenia and if so whether this has a positive effect on clinical outcomes for hip fracture patients.

There is a need to better understand the effect of nutritional supplements on reducing the risks of infections/complications, rehabilitation/hospital stay and, most importantly, mortality in elderly patients. Nutritional supplements may have the potential to significantly improve the quality of life in patients who suffer an unfortunately common ailment in their old age. Furthermore, relatively inexpensive supplements have the possible capability of reducing the cost of treating infections and maintaining hospital beds for increased periods of time.

Additionally, more research is required on when to provide ONSs, for what period of time, how much to give, and the patients who need it the most — those who are malnourished or all patients. Lastly, more studies are required on whether an ONS with higher levels of protein is actually significantly better than an ONS with little or no protein.

Studies evaluating the effects of a variety of different supplements against a control group (hospital food only) on infection and complication rates both in and out of the hospital, functional status measured at different time intervals after the operation, length of hospital, and rehabilitation stay and, finally, mortality are recommended to definitively determine whether or not nutritional supplements are beneficial.

In conclusion, there is very little work that can prove the benefits of elderly patients using nutritional supplements who are suffering from hip fractures. Consequently, more studies are needed to understand the effects of ONSs used in everyday hospital treatment on preventing complications and mortality in patients with hip fractures and reducing hospital stays.

Conflicts of interest

No authors have received anything of value in relation to this work and there are no conflicts of interest.

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