

Metabolism and catabolism in hip fracture patients

Nutritional and anabolic intervention—a review

Margareta Hedström^{1,4}, Olle Ljungqvist^{2,3,4} and Tommy Cederholm⁵

¹Division of Orthopedics, Karolinska University Hospital Huddinge, ²Center of Gastrointestinal Disease, Ersta Hospital, ³Division of Surgery, ⁴CLINTEC, Karolinska Institutet, Stockholm, ⁵Departments of Public Health and Geriatrics, Clinical Nutrition and Metabolism Unit, Uppsala University Hospital, Uppsala, Sweden.

Correspondence MH: margareta.hedstrom@karolinska.se

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ABSTRACT Patients suffering from hip fracture are known to be at risk of catabolism and protein-energy malnutrition. In this review we discuss the pathogenesis of hip fracture-related catabolism per- and postoperatively. We also describe the consequences of malnutrition after a hip fracture and summarize studies that have evaluated the effect of nutritional or anabolic treatment of these patients.

There has been relatively little published on the effects of nutritional and anabolic pharmacological interventions for improvement of nutritional status and on the role of nutritional status in clinical outcomes. Even so, there have been 19 randomized studies in this field. 12 studies evaluated nutritional supplementation or protein supplementation. 6 found improved clinical outcome with fewer complications, faster recovery and shorter length of hospital stay, whereas the others reported no difference in clinical outcome. For pharmacological interventions, the outcomes have been even less clear. Supplementation studies in general appear to be underpowered or suffer logistic problems. Studies of higher scientific quality are needed, and enteral feeding, anabolic treatment and multimodal approaches need to be evaluated in greater depth.

For many patients poor nutritional status represents a key underlying cause for the fracture. Malnutrition is also a main obstacle for recovery. Up to half of elderly patients with hip fractures are already

malnourished on admission to hospital (Akner and Cederholm 2001) and during their hospital stay the intake of energy from food has been shown to be considerably lower than needed (Eneroth et al. 2005). The catabolism continues after a hip fracture, with loss of weight, lean body mass and bone mass (Karlsson et al. 1996, Hedström et al. 1999, Fox et al. 2000). Prominent features of old age are impairment of motor function, i.e. slowing of movement and muscle weakness. Many elderly people have to use all their muscle power to rise from a chair, and even a small impairment in muscle function may dramatically change their rehabilitation capacity. Although the postoperative course depends in part on functional status before a hip fracture, post-fracture loss of lean body mass and strength causes further impairment of the already compromised muscle function. One important predictor for discharge home after a hip fracture is the ability to walk postoperatively (Thorngren et al. 1993). Hence, post-fracture disability is associated with the state of deterioration on admission to hospital, as well as with the trauma-induced catabolism after the fracture.

■ In this review we discuss mechanisms behind the catabolism related to the fracture and operative trauma, and summarize the results of studies designed to prevent catabolism and augment anabolism in hip-fracture patients.

Methods

A Medline (PubMed) search identified 37 articles for “hip fracture and nutritional support”, of which 34 had been published after 1990. A corresponding search for “hip fracture and anabolic treatment” revealed 12 other articles. A wider search was undertaken by choosing the option “related articles” in the database. We also searched the Cochrane Central Register of Controlled Trials, Embase, and also reference lists. From these sources and our own reference files, 19 randomized controlled trials (RCTs) relevant to hip fracture patients were found. 2 studies described the treatment of established protein-energy malnutrition (PEM) in hip fracture patients, whereas the rest did not use PEM as an inclusion criterion. In 12 of the treatment studies, the treatment consisted of food enrichment or of oral supplements in the form of nutritional drinks. 4 studies involved enteral nutrition via a naso-gastric tube or by percutaneous endoscopic gastrostomy (PEG). We found 8 randomized studies in which pharmacological interventions were used, e.g. growth factors or anabolic steroids, either alone or in combination with nutritional supplements (Table).

Indicators of PEM and nutritional status of the hip fracture patient on admission

The definition of PEM and the methods used to identify PEM varied between studies. Anthropometric measurements such as body mass index (BMI) and results of biochemical tests such as insulin-like growth factor-I (IGF-I) and albumin levels in serum were commonly used in the assessment of nutritional status. Many studies reported low BMI in hip fracture patients; for example, in one study 25% of the hip fracture patients had a BMI of < 20 (Bachrach-Lindström et al. 2001). Mean BMI values in a cross-sectional sample of Swedish 78-year-old women and 80-year-old men were found to be 26 and 25, respectively (Björkelund et al. 1997). Low BMI has consistently been shown to be a predictor of increased mortality in elderly patients in general (Flodin et al. 2000).

Some authors have suggested that low serum levels of IGF-I, a peptide hormone mainly produced in the liver, may be a better indicator of PEM than other markers (Campillo et al. 2000).

IGF-I mediates many of the anabolic effects of GH and the hormone exerts multiple insulin-like metabolic effects; for example, it lowers blood glucose, inhibits lipolysis, and retards protein breakdown (Thissen et al. 1999). Hip fracture patients have low IGF-I levels upon admission and these levels remain low up to 6 months after a hip fracture (Hedström et al. 1999, Tidermark et al. 2004).

Peroperative catabolic stress

The inflammatory reaction in response to injury and/or surgical stress leads to catabolism. Injury-induced release of stress hormones and proinflammatory cytokines such as tumour necrosis factor- α , IL-1 β and IL-6 may sustain a prolonged catabolic state characterized by nitrogen loss (Weissman 1990, Cederholm et al. 1997) and insulin resistance, the latter often presenting as hyperglycemia despite elevated levels of insulin, exacerbating the depletion of muscle protein and lean body mass. Although insulin resistance may be physiological in some situations, it is generally not beneficial for recovery (Thorell et al. 1999, van den Berghe et al. 2001). It is not unusual to have delays of more than 36 h before surgery of a hip fracture (Jonsson et al. 1999, Dorotka et al. 2003). During the preoperative period, patients are usually fasting while waiting for surgery. Johnsson et al. (1999) reported a mean intake of only 300 kcal daily before operation of a hip fracture. The fasting itself will induce a state of insulin resistance and catabolism (Ljungqvist et al. 2001), and the trauma induced by the fracture will further aggravate the catabolism.

As the patients with a hip fracture are already in a catabolic state within minutes of their injury, these patients have a different metabolic situation from that in elective surgical patients with a basically normal metabolism before the operation. Thus, it is unlikely that any nutritional intervention in these patients will have the same effects as in the regular elective patient. It is important to study different ways of reducing the preoperative stress in these patients.

Postoperative catabolism

Many studies have reported a loss of total body weight and lean body mass during the first 6 months after a hip fracture (Karlsson et al. 1996, Hedström et al. 1999, Fox et al. 2000). Such weight loss is

related to a lower rehabilitation capability, a longer hospital stay and failure to return to normal life (Sullivan et al. 1990, Lumbers et al. 1996). It has been suggested that hip fracture patients remain in a hypercatabolic state promoted by a residual inflammatory syndrome for up to 3 months after surgery. Fulfilling nutritional needs is highly unusual in this patient group, since most surveys of dietary intake in patients recovering from hip fractures have reported energy intake and protein intake that are too low (Patterson et al. 1992). It is therefore important to determine whether active nutritional treatment postoperatively can improve the long-term outcome.

Intervention trials with nutritional supplementation postoperatively

12 controlled and randomized studies have evaluated the effect of nutritional support after a hip fracture (Table). There is no clear benefit in terms of mortality after protein and energy supplementation, but studies are usually not designed to address possible effects on mortality. However, improvements in clinical outcome—e.g. shorter recovery times, less complications and shorter hospital stays—were found in 6 of the studies (Bastow et al. 1983, Delmi et al. 1990, Tkatch et al. 1992, Schurch et al. 1998, Sullivan et al. 1998). ADL functions were preserved in patients given a protein-rich liquid supplement (Tidermark et al. 2004).

Nutritional treatment may have positive effects on body composition. Protein-enriched nutritional support attenuated the loss of bone mineral density (BMD) in the femur (Tkatch et al. 1992, Shurch et al. 1998) and several of the intervention studies have shown a positive effect on either biochemical or anthropometric indicators of nutritional status (Bastow et al. 1983, Hartgrink et al. 1998, Schurch et al. 1998, Neumann et al. 2004). In the latest meta-analysis update from the Cochrane Collaboration on nutritional supplementation for hip fracture aftercare (Avenell and Handoll 2005), 18 of 50 studies were included, comprising 1,306 patients. Randomized and quasi-randomized trials of oral protein and energy supplementation for mainly older people (aged over 65 years) with hip fracture were selected. The overall conclusion remains that oral multinutrient feed may reduce unfavorable outcome, i.e. death and complications combined,

with a relative risk of 0.52 (95% CI 0.32–0.84). The data are insufficient to suggest recommendation of nasogastric feeding, whereas protein-rich supplementation may reduce long-term complications and the number of days spent in hospital.

Pharmacological intervention trials

Anabolic steroids

3 randomized studies have addressed the effects of treatment with anabolic steroids on functional and body composition recovery after a hip fracture (Table). In one 4-week pilot study, there were no positive effects found on ADL (Sloan et al. 1992, Table). A 1-year study with nandrolone decanoate together with vitamin D and calcium resulted in retained muscle volume and a better function postoperatively (Hedström et al. 2002) (Table). This was also found by Tidermark et al. (2004) who reported a positive effect on lean body mass, ADL and quality of life after nandrolone decanoate treatment in combination with nutritional supplementation for 6 months after a hip fracture (Table). Such therapy is easy to administer but is restricted to women, due to the risk of prostate cancer if given to men.

Recombinant human growth hormone and IGF-I

Likewise, a few studies have addressed the effect of growth hormone (GH) treatment on body composition and clinical function after a hip fracture (Table). A small double-blind study reported a lean body-preserving effect of short-term GH treatment (Hedström et al. 2004) (Table) and another double-blind short-term GH therapy study showed a faster return to prefracture living (van der Lely et al. 2000) (Table). This was in contrast to a recent 6 month-study with oral GH secretagogue given to hip fracture patients who reported no functional improvement from this treatment (Bach et al. 2004) (Table). Moreover, there have been reports of serious side effects of GH treatment in acute critically ill patients (Takala et al. 1999), but not in hip fracture patients when therapy was started 3–4 days postoperatively (Yeo et al. 2003, Hedström et al. 2004). Daily infusions of recombinant IGF-I/IGFBP-3 complex for 2 months in hip fracture

Intervention trials in hip fracture patients postoperatively

Reference	Study design ^a	Patients ^b		Nutritional treatment				Effects	
		No.	PEM	Type	Energy (kcal/d)	Protein (g/d) ^c	Duration	Anthropometry/biochemistry	Function/mortality
Bruce et al. 2003	RCT	109	No	Oral supplement	352	+18	28 d	no difference in weight loss	No effects on mortality, length of hospital stay or Katz index
Delmi et al. 1990	RCT	59	No	Oral supplement	250	+20	32 d		Complications ↓, hospital stay ↓; 24 vs. 40 d.
Neumann et al. 2004	RCT	38 (46)	No	Oral supplement	500	+30 vs +18	28 d	Ss-albumin ↑	No difference in length of hospital stay
Houwing et al. 2004	RCT, DBP	103	No	Oral supplement	500	+40	10 d		Trend for delayed pressure ulcer onset
Espauella et al. 2000	RCT, P	128 (171)	No	Oral supplement	–	+20	60 d		No effect on function or mortality
Schurch et al. 1998	RCT, P	63 (82)	No	Oral supplement	–	+20	6 mo	bone density ↑, s-IGF-1 ↑	Hospital stay (in 1 year) ↓; 33 vs. 54 d.
Tkatch et al. 1992	RCT, P	62 (68)	No	Oral supplement	–	+20	38 d		Complications ↓, hospital stay ↓ in 7 mo; 70 vs. 102 d
Sullivan et al. 2004	RCT	57	No	Enteral or oral feeding	1375		1–2 w	s-albumin ↑	No effect on 6 month complication rate or mortality
Sullivan et al. 1998	RCT	15 (18)	No	Enteral feeding	1400 mL		15 d	no effect	6 mo mortality ↓, 0 vs. 50%
Bastow et al. 1983	RCT	122 (122)	Yes	Enteral feeding	1000	28	~4 w	AMC ↑	Faster rehab; 10 d vs. 12 d and 16 d vs. 23 d in “thin” and “very thin”, respectively
Hartgrink et al. 1998	RCT	101 (140)	– ^d	Enteral feeding	~1500 kcal	~60	1–2 w ^e	hemoglobin ↑, s-albumin ↑	No effect on pressure sore ris
Sloan et al. 1992	RCT, P	29 (31)	No	Nandrolone 2 mg/kg i.m./w	–	–	4 w		No positive or negative effects
Hedström et al. 2002	RCT	51 (63)	No	Nandrolone 25 mg i.m./ third week + vit D			12 mo	bone density ↑, muscle volume ↑	Better hip score and faster gait speed
Tidermark et al. 2004	RCT, P	52 (59)	Yes	Nandrolone 25 mg i.m./ third week	2–400 mL	20–40	6 mo	lean body mass ↑ (nandrolone)	Better ADL (nutrition alone and nandrolon) and quality of life (nandrolon)
Van der Lely et al. 2000	RCT, DBP	76 (111)	No	Growth hormone 20 µg/kg/d			6 w	IGF-I ↑	Barthel index of ADL improved and return to prefracture living if >75 y
Yeo et al. 2003	RCT, DBP	31	No	Growth hormone 0.050 or 0.025 mg/kg/d			2 w	IGF-I ↑	Not studied
Hedström et al. 2004	RCT, DBP	18 (20)	No	Growth hormone ~5.8 IU/day			~4 w	IGF-I ↑, bone density and total lean body mass were preserved	No effect on strength
Bach et al. 2004	RCT, DBP	111	No	Growth hormone secretatogue 25 mg/d			6 mo	IGF ↑	No effect on function or independent living
Boonen et al. 2003	RCT, DBP	30 (33)	No	rhIGF-I/BP-3 0.5 or 1.0 mg/d			2 mo	bone density ↑	Muscle strength ↑ Functional ability ↑

Legends to Table

- ^a RCT – randomized controlled study, P – placebo, DBP – double blind placebo
- ^b Number of patients analyzed per protocol; number of subjects randomly assigned in brackets. PEM – protein-energy malnutrition.
- ^c denotes intended supplementation, without + the figure gives the estimated total intake.
- ^d high-risk patients for pressure sore.
- ^e high rate of tube intolerance
- IGF-1 – insulin-like growth factor-1, AMC – arm muscle circumference.

patients were recently reported to be beneficial for muscle strength and function (Boonen et al 2002) (Table).

Discussion

The data that are available indicate some beneficial effects from nutritional treatment or hormonal support after hip fracture. However, the issue has not been resolved. As shown in the Table (summarizing 19 RCTs), the studies show a great deal of heterogeneity. Some have reported only small numbers of patients, some trials have had short treatment periods, and the outcome variables vary between the studies. The ability of elderly patients to comply with a prescribed nutritional intake varies (Lawson et al. 2000, Bruce et al. 2003). However, a recent Cochrane analysis concluded that total nutrient intake in geriatric patients is increased by nutritional supplementation (Milne et al. 2002).

Although the treatment may induce increases in anthropometric and biochemical variables, the extent to which these relate to function and capacity is unclear. Low BMI or low serum albumin levels have been reported to correlate with mortality in ill people in general, but the causality is often unclear. It is not always certain that nutrition-induced increase in anthropometric and biochemical variables improves the prognosis, or that functional capacity or quality of life is improved. There have, however, been some studies that show such relationships. In the study of Tidermark et al. (2004), the combination of protein-rich supplementation and nandrolone had preservative effects on lean body mass, which was also related to improved ADL function and better quality of life.

Regarding nandrolone or GH treatment, too few studies have been performed to form a firm basis for treatment recommendations after hip fracture. Nandrolone decanoate may turn out to be an option in selected female patients because of its possible positive effects on lean body mass, relative ease of administration, and low costs. There is more of a questionmark over GH, however. It appears less likely to emerge as a feasible treatment alternative.

Several lines of evidence suggest that systemic inflammation following injury/surgery/disease is one delineator of non-response to nutrition treatment (Cederholm and Hellström 1995, Creutzberg et al. 2000, Paillaud et al. 2000). This is not surprising given the fact that inflammation causes insulin resistance; in essence, the patient develops a metabolic situation that is similar to chronic untreated type-2 diabetes (Thorell et al. 1999). Pharmacological modulation of the inflammatory response by use of substances such as thalidomide, pentoxifylline and dronabinol may be one way to promote anabolism and stimulate the appetite in order to achieve improved lean body mass. This remains to be shown.

Physical exercise (Fiatarone et al. 1994) together with nutritional supplementation may be another yet virtually untried way to promote recovery after hip fracture. This method has been evaluated to some extent in case series using the so-called “fast track surgery” programs—a multimodal method to minimize the effect of the surgical stress response (Wilmore and Kehlet 2001). The optimized perioperative approach has been evaluated in a non-randomized study involving 100 consecutive patients with hip fractures; these patients were compared to 100 patients treated conventionally at the same hospital (Rasmussen et al. 2002) and there were fewer complications and a shorter hospital stay. The treatment program consisted of continuous epidural analgesia, oxygen supplementation, early oral nutrition with protein supplementation, and early vigorous mobilization.

Two important issues to consider are why nutritional intervention studies have difficulty in meeting accepted quality criteria, i.e. the Consort statement, and how the scientific quality of the protocols may be improved. Problems appear to converge on the logistics surrounding placebo treatment, the

blinding process, compliance and particularly the intention-to-treat analyses.

Even though there are many uncertain factors in the interpretation of the studies reviewed, the data that are available seem to suggest that nutritional supplements, either alone as balanced or protein-rich liquid nutrient drinks or in combination with hormonal administration, may have positive effects on recovery when given to elderly hip fracture patients. The evidence is still weak, however, (Avenell and Handoll 2005) and further well-designed, well-performed randomized intervention studies are needed to confirm the possible positive effects reported so far.

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