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Original Research

A high-protein diet during hospitalization is associated with an accelerated decrease in soluble urokinase plasminogen activator receptor levels in acutely ill elderly medical patients with SIRS



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ABSTRACT

Acute illness and hospitalization in elderly individuals are often accompanied by the systemic inflammatory response syndrome (SIRS) and malnutrition, both associated with wasting and mortality. Nutritional support and resistance training were shown to increase muscle anabolism and reduce inflammation in healthy elderly. We hypothesized that nutritional support and resistance training would accelerate the resolution of inflammation in hospitalized elderly patients with SIRS. Acutely admitted patients aged >65 years with SIRS were randomized to an intervention consisting of a high-protein diet (1.7 g/kg per day) during hospitalization, and daily protein supplement (18.8 g) and 3 weekly resistance training sessions for 12 weeks after discharge (Intervention, n = 14), or to standard-care (Control, n = 15). Plasma levels of the inflammatory biomarkers soluble urokinase plasminogen activator receptor (suPAR), interleukin-6, C-reactive protein (CRP), and albumin were measured at admission, discharge, and 4 and 13 weeks after discharge. The Intervention group had an earlier decrease in suPAR levels than the Control group: -15.4% vs. +14.5%, $P = .007$ during hospitalization, and -2.4% vs. -28.6%, $P = .007$ between discharge and 4 weeks. There were no significant effects of the intervention on the other biomarkers.

Abbreviations: BMI, body mass index; CG, control group; CRP, C-reactive protein; DEMMI, de Morton Mobility Index; DXA, dual-energy x-ray absorptiometry; IG, intervention group; IL-4, interleukin-4; IL-6, interleukin-6; IFN- γ , interferon- γ ; NRS, nutritional risk screening; ONS, oral nutritional supplement; SIRS, systemic inflammatory response syndrome; suPAR, soluble urokinase plasminogen activator receptor; TNF- α , tumor necrosis factor alpha.

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All biomarkers improved significantly between admission and 13 weeks, although with different kinetics (suPAR: –22%, interleukin-6: –86%, CRP: –89%, albumin: +11%). Nutritional support during hospitalization was associated with an accelerated decrease in suPAR levels, whereas the combined nutrition and resistance training intervention after discharge did not appear to affect the inflammatory state. Our results indicate that improved nutritional care during hospitalization may accelerate recovery in acutely ill elderly medical patients.

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1. Introduction

One-third of patients admitted to emergency wards meet the criteria for the systemic inflammatory response syndrome (SIRS) [1]. The syndrome is defined by the presence of at least two of the following: fever or hypothermia, leukocytosis or leukopenia, tachycardia, and tachypnea [2]. SIRS is a response to a physiological insult, typically an injury or infection, and its early stage is characterized by the systemic release of pro-inflammatory proteins, and an anti-inflammatory response that aims to restore homeostasis [3]. Frequent complications of SIRS include multiple organ dysfunction and a state of shock, and SIRS is associated with high mortality rates [1,3]. The incidence of SIRS and one-month mortality rate is especially high among elderly medical patients [1,4,5].

In elderly medical patients, the pro-inflammatory response in SIRS may be amplified and sustained by inflammaging, the age-associated increase in low-grade systemic inflammation [6]. Elevated levels of interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor alpha (TNF- α) are hallmarks of inflammaging and may tip the balance towards prolonged inflammation [6]. The inflammatory biomarker soluble urokinase plasminogen activator receptor (suPAR) is also strongly associated with age, low muscle mass, and all-cause mortality, suggesting that it may be a useful marker of inflammaging [7–9].

More than 70% of acutely admitted patients older than 65 years are at nutritional risk, which is associated with high mortality [10,11]. Both systemic inflammation and malnutrition can lead to wasting as a result of increased muscle protein catabolism [12]. Loss of muscle mass and strength are associated with poor outcomes, including impaired functional ability, reduced quality of life, hospital readmissions, and mortality [13–15]. Thus, it is necessary to develop strategies to limit wasting associated with acute illness. Interventions consisting of nutritional support and resistance training were shown to increase anabolism, and reduce inflammation in healthy elderly individuals [16–19]. In a randomized controlled study, we have previously investigated the effect of an intervention of high-protein diet and resistance training on muscle mass (assessed by Dual-energy X-ray absorptiometry) in acutely ill elderly medical patients with SIRS [20]. The study showed no effect of the intervention on muscle mass (mean difference of –1.28 kg in the change in whole-body lean mass between the Intervention and Control groups, $P = .32$), or on the secondary outcome measures functional ability and muscle strength [20]. It is possible that inflammatory biomarkers and albumin may be more sensitive measures of the effect of this intervention. In particular, the effect of the intervention on suPAR levels is of interest as it is a strong predictor of mortality and readmissions in medical patients,

and it also reflects muscle mass [21,22]. In contrast to IL-6 and CRP, suPAR is more stable during acute illness or injury and, thereby, may better reflect underlying processes rather than the acute phase response [23,24]. However, it is not known if protein and energy supplementation and resistance training can ameliorate the course of inflammation in elderly patients with SIRS.

In this secondary analysis of a randomized controlled study, the aim was to investigate the effect of a high-protein diet and resistance training on the levels of inflammatory biomarkers in acutely ill elderly medical patients with SIRS. We hypothesized that this intervention would lead to a faster improvement of the inflammatory status in these patients. Our hypothesis was tested using a randomized controlled trial with repeated measures. Acutely ill elderly medical patients with SIRS were randomized to an intervention group or a control group. The intervention group received a high-protein diet during hospitalization followed by daily protein and energy supplementation and three-weekly resistance training sessions for 12 weeks after discharge. The control group received standard care. Plasma levels of suPAR, IL-6, CRP, TNF- α , interleukin-4 (IL-4), and interferon- γ (IFN- γ), and albumin were measured at admission, discharge, and 4 and 13 weeks after discharge.

2. Methods and materials

2.1. Study design and patients

Between April 2013 and February 2014, 29 patients were included in this randomized, controlled, single-blinded intervention study. Fourteen patients were randomized to the Intervention group (IG), and 12 to the Control group (CG), and three additional patients were allocated to the CG for practical reasons, as the training facilities were unavailable in their municipality. The methods of the study, including inclusion criteria, randomization, intervention, data collection, and blinding are described in details elsewhere [20]. In short, patients aged ≥ 65 years fulfilling the criteria for SIRS (the presence of at least two of the following: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; heart rate >90 beats/min; respiratory rate >20 breaths/min or $\text{PaCO}_2 <4.3$ kPa; white blood cell count $>12 \times 10^9/\text{L}$ or $<4 \times 10^9/\text{L}$ or $>10\%$ immature forms [2]) were recruited from the Emergency Department at Copenhagen University Hospital, Amager and Hvidovre, Denmark. The intervention consisted of a high-protein diet (1.7 g protein/kg per day) during hospitalization, and daily protein and energy supplementation (Oral Nutritional Supplement (ONS) containing 18.8 g milk-based protein and 1054 kJ) combined with 3 weekly supervised sessions of progressive resistance training for 12 weeks after discharge. The resistance training exercises consisted of sit-to-stand or knee extension exercise, and the ONS was consumed immediately after the

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