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Does Active Nutritional Interventions Affect Adipokine Secretion in Hip Fracture Operated Elderly Patients?

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Abstract

Background: Adipokines such as ghrelin, leptin, resistin and adiponectin have been proposed as being involved in energetic balance and bone turnover. There is scarce knowledge as to adipokine activity in hip fractured elderly patients in acute settings. We evaluated whether active nutritional support may reflect on adipokines levels and affect outcomes.

Methods: A randomized controlled study measuring adipokine (ghrelin, leptin, resistin and adiponectin) levels in hip fractured geriatric patients receiving active nutritional support was conducted in the Ortho-Geriatric Unit Rabin Medical Center, Israel. The intervention group's energy goal was calculated by repeated resting energy requirements whereas the control group received only standard nutritional support. Measurements were taken pre-operation, 48 h post-operative and on day 7 post-op.

Results: Ghrelin and adiponectin levels showed significant changes in both study groups with no significant change between groups. Ghrelin levels were also significantly higher on day 7 in patients without complications ($p=0.035$). Leptin levels differed between groups ($p=0.038$). In the intervention group, leptin levels decreased initially, then sharply increased, whereas the control group's levels consistently decreased in all 3 measurements. Resistin levels did not change significantly over time.

Conclusion: Ghrelin and adiponectin may play a role in hip fractured patients irrespective of nutritional status whereas, ghrelin levels may also indicate post-operative complications. Leptin may be affected by energetic balance.

Keywords: Hip fracture; Adipokines; Nutritional support; Bone turnover

Background

Hip fractures are a significant health risk of the elderly population in western society and a major cause of morbidity and mortality. In the year 2000, approximately 1.6 million osteoporotic hip fractures occurred worldwide, their incidence and related morbidity is predicted to rise and reach 6.3 million by 2050 [1,2]. Hip fractures carry a significant mortality and morbidity burden with one-year mortality rates as high as 25% [3]. Many factors have been suggested which influence the prognosis of hip fractured patients, one of which is the patient's nutritional status [4,5]. Approximately 50% of elderly hip fractured patients are malnourished on admission to the hospital and numerous others appear so after hospitalization. The deterioration of nutritional status of hospitalized patients can be partially attributed to an inflammatory response, catabolic status, poor intake, pain and medication adverse events. Negative effects of malnutrition include muscle wasting and weakness, impaired mobility, predisposition to decubitus ulcers, pulmonary complications (including atelectasis and pneumonia) and a predisposition to infections.

Evidence has shown a positive effect of active nutritional interventions in acute settings including hip fractured patients [6,7]. Recently, we demonstrated that nutritional support supervised by a dietician and guided by repeated measurements of resting energy requirements using indirect calorimetry, improved outcomes in geriatric patients following hip fracture surgery [8].

Adipokines such as ghrelin, leptin, resistin and adiponectin are cytokines secreted by the adipose tissue and have been suggested to play a role in the energy balance via dual effects on food intake and energy expenditure [9-14]. Ghrelin is an orexigenic protein considered an important gut-brain signal for appetite control and energy balance. By acting on vagal afferents or centrally, ghrelin can activate secretion of orexigenic peptides and inhibit anorexigenic hormones [13-16]. Leptin is the first adipokine documented. It is thought to play a role in the body's energetic homeostasis and assist in maintaining body weight, mostly via hypothalamic receptors [17-19]. Leptin also appears to play a pro-inflammatory role in mediating an immune system response [20,21]. Resistin is a polypeptide secreted from rats' adipose tissue and has been shown to play a role in the metabolic syndrome and insulin resistance [22]. However, in humans, resistin is primarily secreted by peripheral-blood mononuclear cells [23]. Data as to the role of human resistin levels and central/visceral obesity, as well as insulin resistance, is inconclusive. Resistin is considered an inflammatory mediator and a biomarker of cardiovascular (CV) diseases [24,25]. Adiponectin is

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the most abundant peptide secreted by adipocytes and plays a role in obesity-related diseases, including insulin resistance/type 2 diabetes and cardiovascular disease [12]. Studies have advocated adiponectin to have anti-atherogenic and anti-inflammatory effects. In contrast to secretion of other adipokines, adiponectin paradoxically decreases in obesity [26-28].

Limited studies have reported on adipokine secretion and hip fractured elderly patients. Adiponectin but not leptin may increase fracture risk [29]. Admission low leptin levels in hip fractured patients have been found associated with increased post-op myocardial infarction risk [30] and predicted delirium [31]. Gulin et al found that high levels of adiponectin and leptin were associated with all-cause one-year mortality [32]. Fisher et al reported that a high level of resistin was associated with cervical fracture, type 2 diabetes and history of stroke [33]. Our aim was to explore the impact of active nutritional interventions on adipokine (ghrelin, leptin, resistin and adiponectin) secretion in hip fractured operated elderly patients and their relationship to nutritional balance and clinical complications.

Methods

This randomized control study was conducted in the Ortho-geriatric Unit, Department of Geriatrics, Rabin Medical Center, Beilinson Hospital, Israel over a period of 20 months. The local institutional review board approved the study and written informed consent was obtained from all participants prior to randomization. Patients >65 years were included if they had been admitted to the unit within 48h after being diagnosed with a hip fracture, for whom orthopedic surgery was considered treatment of choice. Patients were excluded if they presented to the hospital more than 48h after the injury, were receiving steroids or immunosuppression therapy, had active oncologic disease, had suffered multiple fractures or had been diagnosed with dementia. Patients in need of supplemental oxygen were unable to complete the measurement of resting energy requirements (REE) and were thereby excluded.

Eligible patients were randomly assigned to 2 groups - a tight calorie (intervention) group and control group, within 48 h of the injury and prior to surgery; Randomization was performed using a concealed computer-generated program. All patients received standard preoperative care. The tight calorie group consumed calories with an energy goal determined by repeated REE measurements using indirect calorimetry (IC) (Fitmate, Cosmed, Italy), based on hospital-prepared diets (standard or texture-adapted). Oral nutritional supplements (ONS) were started 24 h after surgery. The amount was adjusted to make up the difference between energy received from hospital food and measured energy expenditure. The ONS provided were either Ensure Plus (Abbott Laboratories) containing 355 kcal/237 ml and 13.5 g protein or Glucerna (Abbott Laboratories) containing 237 kcal/237 ml and 9.9 g protein/237 ml. The patient, family and caregivers were taught the importance of nutritional support and how more attention should be given to personal food preferences. The control group received the usual hospital fare (standard or texture-adapted) and a fixed dose of ONS if one had already been prescribed prior to hospitalization. Hospital-prepared diets provide a mean of 1800 kcal and 80g of protein in the event that the meals are completely consumed by the patients.

All patients underwent IC measurements after fasting for at least 6 h during three time periods: on admission to the study, between 24 and 48 h following surgery and on the 7th day of the study. Measurements were performed by an experienced nurse or dietician. The device was automatically calibrated before each measurement and the REE recorded after 15 minutes. The nutrient intake of each patient was monitored by the research team on a daily basis. Twenty-four-hour food diaries were completed by the medical staff, family and/or caregivers. All meals had a known energy and protein content and the proportion of each component consumed was calculated using a food database program. In addition, the amount of ingested ONS was noted by the medical staff. Before surgery, grip strength in the dominant arm was measured with a hand-grip dynamometer (JAMAR®) with the highest of 3 measurements being recorded. Mid arm circumference (MAC, cm) was measured on the first day of the study using a non-stretchable flexible tape perpendicular to the long axis of the non-dominant arm.

Adiponectin, resistin, leptin and TNFα levels were measured using kits from R&D Systems, Minneapolis, MN, USA whilst ghrelin was measured according to a kit from the Millipore Corporation, Billerica, MA, USA. Blood samples for adipokines were taken on admission, 48 h post-op and on day 7 after enrollment. Routine lab tests including serum glucose, albumin, lymphocyte count and creatinine levels were also collected at these points. Blood was drawn during the early morning after the patient had fasted all night. Demographic, laboratory and clinical data were collected from the patients, caregivers and patient files. Body mass index measured body weight during hospitalization by seat scales, and height was calculated according to measured recumbent knee height. Nutritional status of the patient was assessed on the first day using the Mini Nutritional Assessment (MNA). Cumulative energy balance was assessed either on day 14 or upon discharge including the preoperative period. Comorbidity was assessed retrospectively with the Cumulative Illness Rating Scale for Geriatrics and the Charlson's Comorbidity Index. The Functional Independence Measure scale was used to assess pre-facture functional ability and the Mini-Mental State Examination assessed cognitive function.

Complications included surgical (i.e., local bleeding or the need for repeat surgery); infectious, including pneumonia (based on clinical symptoms and signs and positive chest radiograph), urinary tract infection (based on clinical symptoms and signs and positive urinary cultures) and wound infections (based on clinical symptoms, signs and positive wound cultures); cardiovascular complications, such as myocardial infarction (based on clinical symptoms and signs together with a positive electrocardiogram and elevated enzymes) and congestive heart failure (based on clinical symptoms, signs and compatible chest radiograph); gastrointestinal (i.e., gastrointestinal bleeding); delirium lasting >4 days (based on the Confusion Assessment Method algorithm); deep vein thrombosis (based on clinical features and a positive doppler sonography examination) and the development of new pressure sores (stage 2 and above). Differences between the two groups were assessed using the Student's t test for parametric data and the Chi-square test for categorical data. Changes in adipokine and cytokine levels over time were accessed using the repeated-measures analysis of variance test. The correlation of adipokines with mortality rates was verified using the Cox proportional-hazards model. All calculations were performed using SPSS software (version 12.0, SPSS, Chicago, IL). Results are expressed as mean standard deviation. A p level <0.05 was considered statistically significant.

Results

A total of 230 patients were screened, of whom 51 were found eligible for inclusion into the study. Reasons for non-inclusion included dementia (n=80), oncologic disease (n=17), presentation to hospital >48 h after the injury, (n=14), patients refusal to participate in the study (n=21) and others (n=47). A patient initially recruited to the study group did not undergo surgery and was therefore excluded. Thus, 50 patients were included; 22 in the intervention and 28 in the control group. All patients completed the study.

Baseline characteristics were published earlier [8] (Table 1) and did not significantly differ between groups. Mean age was 83 y, 35% males, cognitive, functional and comorbidity indexes were evaluated with no statistically significant difference found between the groups; 63.6% of the patients in the intervention group and 64.3% in the control group, were well nourished; 36.4% in the intervention group and 35.7% in the control group, were found at risk for malnutrition, differences were not statistically significant. Although, there were no malnourished patients in either group (i.e. MNA <17), 3 patients in the intervention group and 5 in the control group maintained MAC measurements <15th percentile (p=NS). There was no significant difference in type of fracture or procedure between the 2 groups. The waiting time between hospital admission and surgery was not significantly different between the 2 groups (1.4 ± 0.5 days for the intervention group *vs*. 1.4 ± 0.7 days for the control group, p=0.635). During this time period, patients remained in a semi-fasting state while awaiting surgery.

Table 2 summarizes the mean energy and protein values from recruitment prior to surgery and up to day 14. During the first 11 postoperative days (p=0.001), patients in the intervention group displayed a significantly higher mean daily intake of energy and protein compared to the control group Three patients in the control group received additional enteral energy sources: one patient required mechanical ventilation and was fed through a feeding tube while the other two had received ONS at home, on a regular basis, prior to the present admission and continued in the hospital. The length of the hospital stay, and the incidence of complications have been previously published and indicated a lower rate of complications, particular pneumonia, a significant negative correlation between the cumulative energy balance and total complication rate as well as the length of hospital stay in the intervention group [8].

Adipokine kinetics are shown in Table 3. A significant elevation in ghrelin levels in both study groups (Figure 1) and significant changes in leptin levels between the groups (Figure 2) were found. In the intervention group, leptin initially declined and then sharply increased, whereas in the control group, it consistently slowly declined

Variable	Study Group (n=22)	Control Group (n=28)	*p*-value
Age (yrs)	82.27 ± 6.06	83.75 ± 6.43	0.876
Gender Male n (%)	6 (27.3%)	11 (39.3%)	0.318
Female n (%)	16 (72.7%)	17 (60.7%)	
Weight (kg)	64.81 ± 9.52	64/29 ± 11/35	0.86
BMI (kg/m2)	25.18 ± 3.19	24.67 ± 4.42	0.653
Mean serum albumin (mg/dl)	3.23 ± 0.34	3.13 ± 0.27	0.282
Mean blood glucose (mg/dl)	121.54 ± 22.52	118.17 ± 21.09	0.589
MNA	24.84 ± 2.57	24.50 ± 2.97	0.672
CCI	0.81 ± 1.05	1.39 ± 1.13	0.073
CIRS-G	7.45 ± 3.59	7.39 ± 2.60	0.944
FIM	80.00 ± 17.62	79.1 ± 17.17	0.863
MMSE	25.16 ± 4.86	23.72 ± 5.19	0.375

Data are expressed as mean ± standard deviation.
Abbreviations: BMI, body mass index; MNA, Mini-Nutritional Assessment; CCI, Charlson's Comorbidity Index; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; FIM, Functional Independence Measure; MMSE, Mini-Mental State Examination.

Table 1: Baseline characteristics of study participants.

Parameter	Study group (n=22)	Control group (n=28)	*P*-value
Mean energy delivered/day (kcal/day)	1121.31 ± 299.05	777.09 ± 301.23	0.001
Mean ONS delivered energy/day (kcal/day)	220.33 ± 147.19	94.57 ± 233.82[a]	0.845
Mean protein delivered/day (g/day)	55.90 ± 18.14	37.41 ± 12.44	0.001
Mean daily energy balance (kcal)	-176.90 ± 273.16	-490.67 ± 355.17	0.104
Cumulative energy balance (kcal)	-1229.93 ± 1763	-4975.55 ± 4368	0.001

[a]Included 1 patient who required mechanical ventilation and received 1500kcal/day via tube-feeding. Data are expressed as mean ± standard deviation. REE, resting energy expenditure; kcal, kilocalories; ONS, oral nutritional supplements.

Table 2: Nutritional and energetic balance.

	Study Group				Control Group				P value between groups
	N	Pre-Operation	48h Post Operation	7th day of the study	N	Pre-Operation	48h Post Operation	7th day of the study	
Ghrelin (pg/ml)	21	925.3 ± 373.5	1061.3 ± 570.2	1249.7 ± 691.6	27	919.5 ± 551	955.3 ± 607.4	1031.1 ± 685.9	N.S.[a]
Leptin (pg/ml)	22	16601 ± 9814	8291 ± 4812[b]	10801 ± 7511	27	15754 ± 11084	12390 ± 10081[b]	10123 ± 7990	N.S.
Resistin (ng/ml)	21	19.3 ± 7.8	19.0 ± 7.87	19.2 ± 7.6	28	12.8 ± 3.9	14.3 ± 4.2	14.6 ± 5.3	N.S.
Adiponectin (μg/ml)	21	9127 ± 7481	4050 ± 1993	5970 ± 2301	26	10736 ± 8711	6042 ± 4310	7601 ± 5149	N.S.[c]

[a]Significant increase (p<0.04) in serum Ghrelin levels from day 1 to day 7 in both study and control groups.
[b]Significant change between the study and control group after 48h (p=0.038).
[c]Significant decrease (p<0.001) in serum adiponectin levels from day 1 to day 7 in both study and control groups.
N.S.- non significant

Table 3: Adipokine levels pre operation, 48 h post operation and on the 7th day.

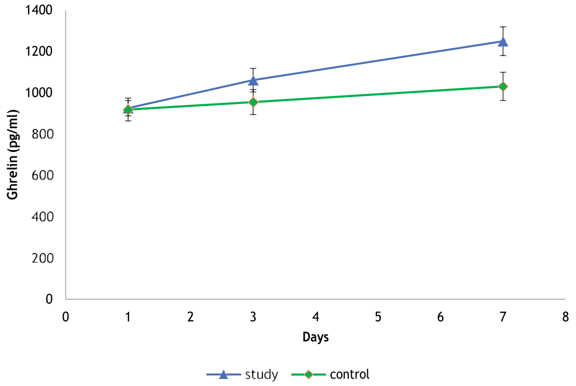
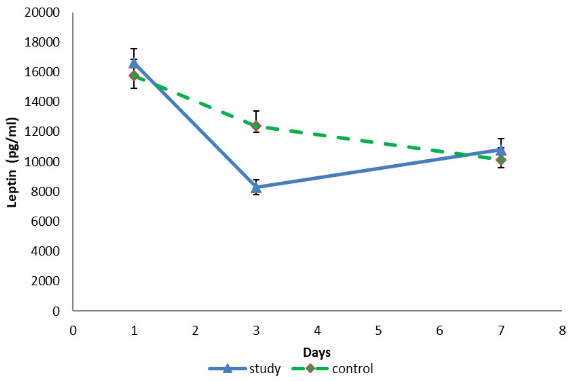


Figure 1: Ghrelin change over time.



Leptin change over time showing a significant decline and then increase in the study group (p=0.038).

Figure 2: Leptin levels between the groups.

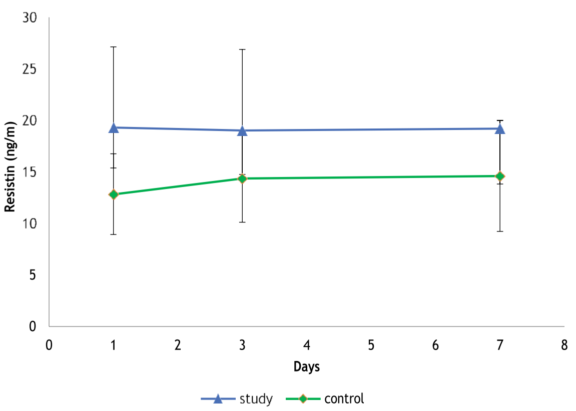


Figure 3: Resistin change over time.

in all 3 measurements. We found no statistically significant differences between the groups on the third measurement of leptin. Resistin did not change significantly in either group (Figure 3). Adiponectin levels changed significantly (p=0.001) in both groups (Figure 4). Most of the change was attributed to a decline in adiponectin levels on day 3. There was no significant difference in adiponectin levels between the two groups. Ghrelin levels on day 7 were significantly higher in

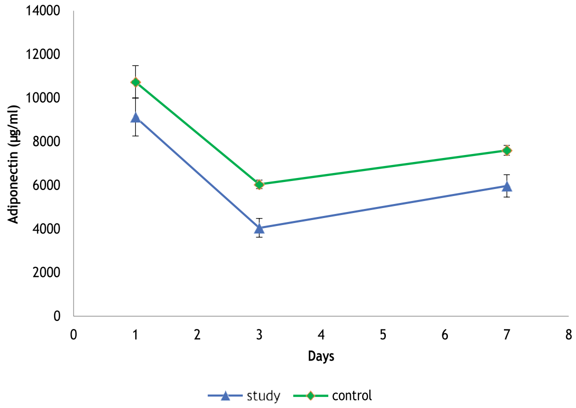


Figure 4: Adiponectin change over time.

patients without complications compared to those with complications (p=0.035) which was primarily attributed to infections (urinary tract or pneumonia). We found no other correlations between adipokine levels, length of hospital stay or complications during the trial period.

Discussion

Overall, the adipokine kinetics levels did not significantly differ between the study groups. However, it seems that the adipokines ghrelin and leptin may be influenced from energetic balance. The elevation in ghrelin levels was also significantly lower for patients with complications during hospitalization. Adipokines are mediators secreted from the adipose tissue which plays a role in obesity, related morbidity and energetic homeostasis via autocrine and paracrine mechanisms. Ghrelin, other than its role in appetite control and energy balance may help regulate cardiovascular function, immune system and bone physiology [34-38]. Previous publication have demonstrated Ghrelin role in osteoblastic proliferation [36]. This may explain the elevation of Ghrelin in both study groups. Contrary to previous reports on rise of Ghrelin levels in states of negative energetic balance [35,39,40], we observed in the intervention group, an opposite trend toward a steeper ghrelin elevation. A possible explanation is that ghrelin may play a role in bone recovery, which was accelerated due to a lower energetic deficit in the study group compared to the control group. Ghrelin levels were significantly lower in patients with complications during hospitalization. These results are surprising considering that previous published studies report the elevation of ghrelin in states of systemic inflammation and in ICU patients [38,41]. Geriatric patients are known to exhibit a slower and lower response of the immune system to acute stress [42], although the nature of the complication, which was mostly mild, may not have been enough to induce ghrelin elevation.

Leptin involvement in bone homeostasis has been suggested in several previous studies with a negative feedback control of leptin on bone remodelling. A previous study by Di Monaco et al. of 74 women with osteoporotic hip fractures observed a negative correlation between leptin and bone density [43]. In a study of post hip fractured patients, osteocalcin, a marker for bone regeneration, was found to correlate with leptin [44]. Other studies have produced conflicting results as to the correlation between leptin and osteocalcin [45-47]. In our study, leptin levels in the intervention group at first declined, then sharply increased whereas, all 3 measurements in the control group the levels consistently slowly declined. Perhaps a lower acute inflammatory response in the intervention group may explain its primary decline but, in our study, we found no evidence to support this theory. These results may support the theory of leptin's negative feedback on bone formation and resorption. The escalated elevation in the intervention group may suggest leptin's role in the body's energetic homeostasis.

A previous study of patients post hip fracture observed elevated resistin levels in cervical fractures [33]. A study of elderly patients post hip fracture, found that osteocalcin concentration is inversely associated with resistin [44]. The results of our study did not show a significant change in resistin levels in either of the study groups. Several studies reporting on animal models have suggested that adiponectin plays a role in bone homeostasis. Though, a previous study suggested that elevated levels of adiponectin correlate with a higher fracture risk in elderly men, its role in human bone homeostasis is still unclear [29]. We observed a significant decline in adiponectin levels on day 3 in both study groups. These finding may support the theory of adiponectin's biphasic behavior in response to acute stress [47]. The short duration of the decline and the absence of change between the groups, suggests that adiponectin has no significant role in bone homeostasis or energetic balance in elderly patients post hip fracture.

The major limitation of this study is its short duration and relatively small sample base. The patients were not followed during their rehabilitation after hospital discharge. We hypothesis that the cytokine storm, shortly after a hip fracture operation [48], probably masked the changes of the adipokines secretion and the effect of the nutritional intervention. A longer follow-up might have confirmed the differences in adipokine secretions between groups. Another limitation is the relatively good nutritional status of the study participants, partially due to the exclusion criteria, i.e. active cancer and dementia which prevented many frail elderly patients from entering the trial. This, however, did not prevent most patients to be in a significant energetic deficit during the trial. We do not expect the results to change significantly in patients with poorer nutritional balance for whom the number of confounders will probably be higher due to a more significant morbidity.

Conclusion

In conclusion, we found no correlation between improved energy balance in geriatric hip fractured patients and adipokine levels. However, as noted, several changes in adipokine behaviors were observed. Differences may be the results of adipokine involvement in bone homeostasis and inflammatory states. A larger scale research study with a longer follow-up period is needed to expand our knowledge of these fascinating cytokines and their interactions with nutritional support.

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