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Inflammatory Cytokine Levels and Depressive Symptoms in Older Women in the Year after Hip Fracture: Findings from the Baltimore Hip Studies

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Abstract

OBJECTIVES—Determine whether interleukin 6 (IL-6) or soluble tumor necrosis factor α receptor 1 (sTNF- α R1) are associated with depressive symptoms in the year after hip fracture

DESIGN—Prospective cohort

SETTING—Three Baltimore-area hospitals

PARTICIPANTS—Community-dwelling women aged ≥ 65 years, admitted with a new, non-pathological fracture of the proximal femur (n=133).

MEASUREMENTS—At 2, 6 and 12 months postfracture, serum was analyzed for IL-6 and sTNF- α R1, and depressive symptoms were measured using the 15-item Geriatric Depression Scale (GDS). Generalized estimating equations were used to model the longitudinal relationship between IL-6 and sTNF- α R1 and GDS score. We also examined whether lower extremity function, as measured by Lower Extremity Gain Scale (LEGS), explained the relationship between IL-6, sTNF- α R1 and GDS score.

RESULTS—Patients in the highest categories of IL-6 (≥ 5.14 pg/ml) and sTNF- α R1 (≥ 2421 pg/ml) had the highest GDS scores in the year postfracture (p=0.09 for both). At 12 months postfracture, those in the highest IL-6 and sTNF- α R1 categories had GDS scores that were on average 1.9 (95% confidence interval [CI]: 0.4, 3.4; p=0.01) and 1.4 (95% CI: -0.1, 3.0; p=0.07)

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Conflict of Interest

Author Contributions: Maya Matheny: data analysis, data interpretation, manuscript preparation; Ram Miller: data interpretation, manuscript preparation; Michelle Shardell: data interpretation, manuscript preparation; William Hawkes: manuscript preparation; Eric Lenze: manuscript preparation; Jay Magaziner: study design, manuscript preparation; Denise Orwig: study design, manuscript preparation.

points higher than those in the lowest category, respectively. Adjusting for LEGS score, the mean difference in GDS scores for highest versus lowest IL-6 categories was 1.6 (95% CI: 0.2, 3.0; $p=0.02$) points at 12 months.

CONCLUSION—Results from these exploratory analyses support a role for inflammation in the pathophysiology of depressive symptoms after hip fracture. Depressive symptoms in the context of elevated cytokines may represent a sickness syndrome that is chronic in some individuals. Further research should establish the cause and effect of this relationship as well as long-term correlates.

Keywords

depressive symptoms; cytokines; hip fracture; Geriatric Depression Scale; elderly

INTRODUCTION

As the world's population ages, the incidence of hip fractures is predicted to increase worldwide. Globally, more than 1.6 million fractures occur annually, and in the United States, over 350,000 persons aged 65 years and over are affected by hip fractures (1, 2). The patients who survive the hip fracture and surgical repair experience tremendous levels of disability, with 25 to 75% of patients who were ambulatory prior to fracture no longer able to walk without assistance or regain their previous level of independent living within the year following fracture (3–5).

In addition to the physical disability resulting from hip fractures, there are also psychological and immune sequelae. The onset of disabling medical illness, such as hip fracture, is one of the most important risk factors for a major depressive episode or depressive symptoms in elderly persons (6, 7). Rates of depression after hip fracture are reported to vary from 9–47% (8), and depressive symptoms and major depressive disorder are the highest immediately following the fracture (9).

On the physiologic level, inflammatory cytokine levels have been observed to increase following trauma and surgery, including after hip fracture (10–12). Elderly patients have an increased IL-6 response to surgical trauma compared with young adults (10). In the elderly hip fracture population, cytokine levels may remain high up to one year postfracture with median interleukin-6 (IL-6) concentrations of 7.05 pg/ml at 12 months (13).

Depressive symptoms are associated with systemic immune activation, characterized by increased production of pro-inflammatory cytokines (e.g., interleukin 1 beta (IL-1 β), IL-2, IL-6, and tumor necrosis factor alpha) by peripheral blood mononuclear cells, in addition to a host of other upregulated immune components (e.g., an acute phase protein response and excessive secretion of pro-inflammatory cytokines, prostaglandins and nitric oxide) (14–16). Evidence from the field of psychoneuroimmunology suggests that complex, multi-directional interactions among the immune, central nervous and endocrine systems, initiated by physical and psychological stressors, explain the increased production and release of pro-inflammatory cytokines observed in patients with major depression (17–19).

The pro-inflammatory cytokines IL-1 β , IL-6 and TNF- α have been identified by many studies as important components in the pathophysiology of depressive symptoms (20). In one recent meta-analysis, positive associations were reported between IL-1 β , IL-6 and CRP and depression (21). In a second meta-analysis of 24 cytokine studies, subjects who met diagnostic criteria for major depressive disorder had elevated levels of IL-6 and TNF- α (22). Several large scale epidemiologic studies have examined the prospective relationships between markers of systemic inflammation and depressive symptoms in adult populations

(23, 24). However, findings in older adults are limited, and there are no studies in elderly persons who have had a hip fracture and may be at increased risk for depression.

Studies of inflammatory cytokine levels and depressive symptoms are important in the field of hip fracture research, as both have been studied independently in relation to functional recovery after hip fracture. Increased levels of inflammation have been associated with poor recovery of function in hip fracture patients. Miller and colleagues concluded that higher serum levels of IL-6 were associated with poorer recovery of performance of lower extremity function among female hip fracture patients in the year following fracture (13). They also suggested that reduced muscle strength may better explain the poorer recovery of lower extremity function in patients with higher levels of IL-6 (25).

This study was an exploratory analysis conducted to estimate the relationship between levels of inflammatory cytokines and depressive symptoms in the year after hip fracture surgery. Additionally, lower extremity performance was examined as a potential mediator of the relationship between postfracture inflammatory cytokine levels and depressive symptoms. The present findings present a focused extension of prior work linking inflammation to depression, which would be of interest to researchers/clinicians who study age-related disorders.

METHODS

Study Design

Patients were drawn from the fourth cohort in the Baltimore Hip Studies (BHS-4), a randomized clinical trial which tested the feasibility of the Exercise Plus Program compared to usual care in hip fracture patients (26, 27). The BHS-4 study was a two-arm randomized clinical trial with hip fracture patients assigned to either usual care (no intervention) or a supervised home-based exercise program that continued for one year post-hip fracture (The Exercise Plus Program). The exercise program began at the end of the usual post-acute therapy period and contained both strength training and aerobic components. Participants were expected to exercise 5 days per week for 45 minutes each day, and the program consisted of a combination of supervised and independently performed exercise sessions. The intensity and strength of the exercises were increased gradually by the trainers in a standardized way. The frequency of the supervised exercise sessions decreased throughout the year as participants became more able to exercise independently. For this analysis, data were aggregated from both treatment and usual care groups, and, in the randomized controlled trial, there was no effect of the active treatment on depressive symptoms (27). Recruitment was initiated in 3 hospitals in the Baltimore area in November 1998 and ended in September 2004. Participants were enrolled within 15 days of the hip fracture. Baseline measurements and pre-fracture data (questionnaire, performance measures and blood draw) were collected within 22 days post-hip fracture and follow-up data were collected at 2, 6 and 12 months postfracture.

Participants

Eligibility was determined through a medical chart review, medical assessment, and cognitive screen. BHS-4 enrolled 180 community-dwelling female hip fracture patients 65 and older who had a non-pathologic fracture within 72 hours of admission and surgical repair of the fracture. Additional eligibility criteria included ability to walk without human assistance prior to the fracture, no medical conditions contraindicated with exercise, and a score of ≥ 20 on the Mini-Mental State Examination (MMSE) (28). Due to safety concerns of older adults exercising independently in the home, the stringent set of study inclusion criteria resulted in only 243 of the 1,276 (19%) screened hip fracture patients being eligible;

however, 74% of eligible women enrolled in the trial. The final sample for this analysis consisted of the 134 unique BHS-4 participants who had both serum cytokine concentration measurements and Geriatric Depression Scale measurements at one or more follow-up visits (2, 6, and 12 months). Institutional Review Board approvals were obtained from the University of Maryland, School of Medicine as well as the study hospitals, and all enrolled subjects provided their own informed consent.

Measures

Depressive Symptoms and Cytokine Measurement—Two, 6- and 12-month depressive symptoms were measured using the 15-item Geriatric Depression Scale (GDS) (29). At the 2-, 6- and 12-month evaluations, serum was collected on 96, 108, and 92 participants, respectively. Sera from these participants were stored at -70°C . IL-6 and sTNF- α R1 levels were measured in serum that had been previously thawed using commercially available enzyme-linked immuno-sorbent assay (ELISA) kits (R&D systems, Minneapolis, MN). For IL-6, the inter-assay CV was 3.44% and the intra-assay CV was 4.37%. For sTNF- α R1, the inter-assay CV was 2.98% and the intra-assay CV was 5.47%.

Covariates—The medical record was reviewed to obtain the patient's age and the number of medical comorbidities. Height and weight were used to calculate body mass index. Treatment group was based on whether the patient had been randomly assigned to the exercise or control groups for the trial. Cognitive status was assessed at baseline using the Mini-Mental State Examination (MMSE) (28). Because elders with worse function may be more likely to manifest depressive symptoms (30, 31), the Lower Extremity Gain Scale (LEGS) score (32) during the follow-up period was also included as a covariate. The LEGS is a summary measurement of timed performance in nine tasks developed to evaluate lower extremity function in hip fracture patients. Performance in each of these tasks was scored on a scale of 0–4, resulting in a total score between 0 and 36. A higher LEGS score indicates better performance.

Analytic Strategy

Participants had to have both a serum cytokine measurement and GDS score at one or more study follow-up visit(s) to be included in this analysis. The analytic sample size consisted of 134 unique participants. For IL-6, this was comprised of 51 participants with both a cytokine and GDS measured at all three follow-up visits, 53 with both a cytokine and GDS measured at two follow-up visits, and 30 with both a cytokine and GDS measured at only one follow-up visits ($134=51+53+30$). For sTNF- α R1, this was comprised of 53 participants with both a cytokine and GDS measured at all three follow-up visits, 52 with both a cytokine and GDS measured at two follow-up visits, and 29 with both a cytokine and GDS measured at only one follow-up visit ($134=53+52+29$).

Serum levels of IL-6 and sTNF- α R1 at the baseline evaluation are more likely to reflect a normal physiological response to the trauma of hip fracture and subsequent surgical repair, and not a prolonged inflammatory process, thus the analysis focused on the relationship between cytokines and GDS at the follow-up visits (2-, 6-, and 12- months post-enrollment) (33, 34). This approach is consistent with previous work from our group (13). Patients were divided into groups based on their serum IL-6 and sTNF- α R1 levels over the 2-, 6-, and 12-month time points of the follow-up period (IL-6: low group: $\text{IL-6} \leq 2.42$, middle group $2.42 < \text{IL-6} < 5.14$, and high group ≥ 5.14 pg/ml; and sTNF- α R1: low group: $\text{sTNF-}\alpha\text{R1} \leq 1734$, middle group: $1734 < \text{sTNF-}\alpha\text{R1} < 2421$, high group: $\text{sTNF-}\alpha\text{R1} \geq 2421$ pg/ml). These cut-points represent the IL-6 and sTNF- α R1 tertile levels of all the observations over the 2 to 12 month follow-up period, therefore ensuring that approximately equal numbers of observations were included in each cytokine group over the follow-up period (13, 25). These

categories are not interpreted as time-specific tertiles; however, this approach ensured a sufficient sample size in each category at each time-point while accurately accounting for patients' changes in cytokine levels.

Generalized estimating equations (GEE) (35) were used to model the longitudinal relationship between IL-6 and sTNF- α R1 category at the 2, 6 and 12 month follow-up evaluations and GDS scores. The GEE analytic method uses data from all visits with both a GDS and cytokine measure and enables performing longitudinal analyses when some study visits are missing. This method can account for possible correlations in repeated measures over time and is suitable for exploring differences in values measured at different times. Generalized F tests were used to compare GDS scores over time between those in the midlevel and high IL-6 and sTNF- α R1 categories to the lowest (reference) IL-6 and sTNF- α R1 group, respectively. Time-specific t-tests were performed to compare IL-6 and sTNF- α R1 group scores at each time point. The models were adjusted for age, Charlson Comorbidity Index score, MMSE score, treatment group (exercise versus control). In order to examine the role of lower extremity function as a potential mediator of the relationship between inflammation and depressive symptoms additional models adjusted for lower extremity performance as measured by the LEGS score. Analyses were performed using SAS, version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Demographic and medical characteristics of the study sample are summarized in Table 1. As the table shows, the sample was representative of hip fracture patients in terms of age, race, and fracture type, but relatively healthier and more cognitively intact as required by the study inclusion criteria. The majority of post-operative complications were listed as "other" (27%), though 4% of participants experienced confusion or disorientation, 3% experienced urinary tract infections and 2% had wound hematomas/bleeding.

After adjusting for covariates, patients in the highest categories of IL-6 and sTNF- α R1 had marginally higher average GDS scores than the lowest categories during the follow-up period, but the result was not statistically significant at the $\alpha=0.05$ level ($p=0.09$ for both). GDS scores did not differ significantly over the follow-up period between patients in the middle and lowest categories of IL-6 ($p=0.78$) or sTNF- α R1 ($p=0.68$). The difference in mean GDS scores between high and low IL-6 groups was greatest at 12 months postfracture; when adjusting for covariates, on average those in the highest IL-6 group scored 1.9 (95% CI 0.4, 3.4; $p=0.01$) points higher on the GDS (Figure 1). For sTNF- α R1, the difference in GDS score between high and low sTNF- α R1 groups was also greatest at 12 months postfracture, when adjusting for covariates, on average those in the highest sTNF- α R1 group scored 1.4 (95% CI -0.1, 3.0; $p=0.07$) points higher on the GDS (Figure 2).

When additionally adjusting for Lower Extremity Gain Scale (LEGS) score, the difference in mean GDS scores between high and low IL-6 groups was attenuated by 16% (Figure 3). When adjusting for covariates, on average those in the highest IL-6 group scored 1.6 (95% CI 0.2, 3.0; $p=0.02$) points higher on the GDS at 12 months postfracture. GDS scores did not differ significantly between middle and low IL-6 groups ($p=0.28$), between high and low sTNF- α R1 groups ($p=0.39$) or between middle and low TNF- α R1 groups ($p=0.32$) (Figure 4).

DISCUSSION

In the current analyses, we examined whether inflammatory cytokine levels were associated with depressive symptom levels, measured by GDS scores, in the year following hip

fracture. We found that hip fracture patients in the highest group of inflammatory cytokine levels for both IL-6 and sTNF- α R1 had higher levels of depressive symptoms than those in the lowest group, particularly at 12 months postfracture. After adjusting for lower extremity performance, measured by LEGS score, GDS scores for hip fracture patients in the highest IL-6 category were attenuated but remained significantly higher than those in the lowest IL-6 category at 12 months postfracture.

Some research has suggested that depressive symptoms after hip fracture are highest in the immediate post-fracture period, with a fairly rapid decline in the subsequent 2 months, likely representing a relatively acute stress response (8, 9, 36, 37). By four to six months postfracture, most patients have reached their recovery plateau in depressive symptoms (37). In contrast, our results suggest that chronically high levels of inflammation are predictive of persistently elevated depressive symptoms for up to a year postfracture, suggesting a different and more chronic pathophysiological process. Depressive symptoms in the context of elevated cytokines might represent a chronic sickness syndrome and not reaction to disability.

Findings such as these could also point to biological mechanisms underlying the occurrence of depressive symptoms after hip fracture. Physical and psychological stressors stimulate transient increases in pro-inflammatory cytokine levels, with most pronounced effects on IL-6 (38, 39). Physical and psychological stressors also stimulate hypothalamo-pituitary-adrenal (HPA) axis and sympathetic nervous system activity, leading to the production of catecholamines and corticosteroids (38–41). Stress hormones can directly modulate immune function (e.g., cytokine production) by binding to their receptors on the surface of immune cells, or by other indirect mechanisms which dysregulate immune activity (18). Cytokines that are produced peripherally are also able to cross the blood-brain barrier and stimulate HPA activity by way of increased corticotrophin-releasing hormone production from the median eminence of the hypothalamus (18, 42–44). An avenue of future research would be to examine postfracture levels of related endogenous mediators (e.g., markers of HPA axis activity such as adrenocorticotrophic hormone or cortisol) to help uncover the biological mechanisms underlying the relationship between inflammation and depressive symptoms after hip fracture.

Since loss of physical function is one of the most significant consequences of a hip fracture, results of studies that help to uncover biological mechanisms underlying poor recovery of function after hip fracture are of great importance. Because elders with worse function may be more likely to manifest depressive symptoms (30, 31, 45), we adjusted for lower extremity performance in this analysis. After doing so, the association between higher levels of IL-6 and GDS scores was attenuated by higher scores (i.e., better performance) on the LEGS. This suggests that the association of IL-6 levels and depressive symptoms may be partially explained by lower extremity functional recovery. The exact nature of the interplay among all three variables (depressive symptoms, inflammatory cytokine levels and functional recovery) remains to be elucidated. However, the results agree with a vast literature supporting a relationship between depressive symptoms and functional recovery in older adults (46–48), and our results suggest that prolonged inflammation is an important variable in this relationship.

These results must be viewed in the context of the following limitations. The GDS is not a diagnostic instrument, though it is appropriate for screening and identification of older patients who may be at risk for developing depressive disorders. Regarding the study sample, only 19% of hip fracture patients identified for the study were eligible (27). Hip fracture patients enrolled in this study were quite robust compared to the general hip fracture population, in that they were more cognitively intact, suffered from fewer comorbid

conditions, and must have been able to perform the study's exercise intervention, thus making the findings from this sample less generalizable to the hip fracture population. Also, the majority of patients included in these analyses were white women and thus we are unable to assess whether similar associations exist in men or in women of other ethnicities. A final limitation was the inclusion of hip fracture patients with MMSE scores as low as 20; due to the lack of validity on the MMSE, participants with a score of 20 may have significant cognitive decline if investigated using more sensitive cognitive measures. Because MMSE is an important confounder, we included it in the analysis. Even with MMSE scores as low as 20, these patients had cognitive function that was good enough to participate in the year-long exercise trial. Additionally, we would like to generalize to a population of female hip fracture patients with cognitive decline. Indeed, chronic inflammation post hip fracture might predict cognitive impairment as well as depressive symptoms.

Findings such as these underscore the importance of routine screening, evaluation and treatment of depression and depressed mood in rehabilitation settings during the postfracture recovery period. Identifying subgroups of hip fracture patients with higher levels of depressive symptoms is important because of the impact of depression on level of recovery and length of rehabilitation. Patients with depression due to disability require longer rehabilitation, and prevalence and persistence of depressive symptoms are risk factors for poor functional recovery postfracture (36, 47, 49). Finally, the relationship between depression and inflammation also has important implications for treatment, as depressed patients with increased levels of inflammatory biomarkers have been found to be more likely to exhibit treatment resistance (50). A better understanding of this chronic immune dysregulation after hip fracture is needed, in order to develop new treatment targets for both depressive symptoms and functional recovery. Further research should establish the cause and effect of this relationship as well as long-term correlates.

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Figure 1.

Estimated Mean GDS Scores by Time-Dependent IL-6 Group. The difference in mean Geriatric Depression Scale (GDS) scores between highest and lowest IL-6 groups was greatest at 12 months postfracture. When adjusting for covariates, on average, hip fracture patients in the highest IL-6 group scored 1.9 (95% CI 0.4, 3.4; $p=0.01$) points higher on the GDS than those in the lowest IL-6 group. Covariates included age, body mass index, Charlson Comorbidity Index score, intervention group, and Mini-Mental Status Examination score. The normal range for the GDS is 0 to 15. Gray = low IL-6 group (≤ 2.42 pg/ml); Diagonal = middle IL-6 group (2.42 pg/ml $<$ IL-6 < 5.14 pg/ml); Black = High IL-6 group (≥ 5.14 pg/ml)

Figure 2.

Estimated Mean GDS Scores by Time-Dependent sTNF- α R1 Group. The difference in mean Geriatric Depression Scale (GDS) scores between highest and lowest sTNF- α R1 groups was greatest at 12 months postfracture. When adjusting for covariates, on average, hip fracture patients in the highest sTNF- α R1 group scored 1.4 (95% CI -0.1, 3.0; $p=0.07$) points higher on the GDS than those in the lowest sTNF- α R1 group. Covariates included age, body mass index, Charlson Comorbidity Index score, intervention group, and Mini-Mental Status Examination score. The normal range for the GDS is 0 to 15. Gray = low sTNF- α R1 group (≤ 1734 pg/ml); Diagonal = middle sTNF- α R1 group (1734 pg/ml $<$ sTNF- α R1 $<$ 2421 pg/ml); Black = High sTNF- α R1 group (≥ 2421 pg/ml)

Figure 3.

Estimated Mean GDS Scores by Time-Dependent IL-6 Group Adjusted for LEGS Score. After additionally adjusting for Lower Extremity Gain Scale (LEGS) score, the difference in mean Geriatric Depression Scale (GDS) scores between high and low IL-6 groups was slightly attenuated. When adjusting for covariates, on average, those in the highest IL-6 group scored 1.6 (95% CI 0.2, 3.0; $p=0.02$) points higher on the GDS at 12 months postfracture. Covariates included age, body mass index, Charlson Comorbidity Index score, intervention group, and Mini-Mental Status Examination score. The normal range for the GDS is 0 to 15. Gray = low IL-6 group (≤ 2.42 pg/ml); Square = middle IL-6 group (2.42 pg/ml $<$ IL-6 < 5.14 pg/ml); Black = High IL-6 group (≥ 5.14 pg/ml)

Figure 4.

Estimated Mean GDS Scores by Time-Dependent sTNF-αR1 Group Adjusted for LEGS Score. After additionally adjusting for Lower Extremity Gain Scale (LEGS) score, mean Geriatric Depression Scale (GDS) scores did not differ significantly between high and low sTNF-αR1 groups ($p=0.39$) or between middle and low TNF- αR1 groups ($p=0.32$). The model was also adjusted for age, body mass index, Charlson Comorbidity Index score, intervention group, and Mini-Mental Status Examination score. The normal range for the GDS is 0 to 15. Gray = low sTNF-αR1 group (≤ 1734 pg/ml); Diagonal = middle sTNF-αR1 group (1734 pg/ml < sTNF-αR1 < 2421 pg/ml); Black = High sTNF-αR1 group (≥ 2421 pg/ml)

Table 1**Demographic and Medical Characteristics at Baseline (N=134)**

Age, mean (SD), y	81.7 (6.7)
White, No. (%)	130 (96.3)
Married, No. (%)	47 (34.8)
Anesthesia risk rating, mean (SD)	2.7 (0.5)
Body mass index (kg/m ²), mean (SD)	23.8 (4.2)
Charlson comorbidity index score, mean (SD)	1.1 (1.3)
Fracture site, No. (%)	55 (40.7)
Intertrochanteric	73 (54.1)
Subcapital	5 (5.2)
Subtrochanteric	
Geriatric Depression Scale score [*] , mean (SD)	2.3 (2.5)
Length of hospital stay, mean (SD)	4.0 (1.4)
Lower Extremity Gain Scale score at 2 months [†] , mean (SD)	23.3 (6.5)
Mini-Mental Status Examination score, mean (SD)	27.0 (2.5)
Post-operative complications, No. (%)	6 (4.4)
Confusion or disorientation	1 (0.7)
Pulmonary embolism	1 (0.7)
Renal failure	2 (1.5)
Shock post-op	4 (3.0)
Urinary tract infection	3 (2.2)
Wound hematoma/bleeding	37 (27.4)
Other complications	

kg/m² = kilograms per meter squared

^{*} Range for Geriatric Depression Scale: 0–15

[†] Lower Extremity Gain Scale Score measured at 2 month follow-up visit (n=113); range: 0–36