

Cytokines and C-Reactive Protein Production in Hip-Fracture-Operated Elderly Patients

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Background. The study aim was to determine the kinetics of serum pro- and anti-inflammatory cytokines and C-reactive protein (CRP) in hip-fracture patients over a month postfracture, and their relationship to postoperative (postop) complications and cognitive level.

Methods. Forty-one elderly hip-fracture patients were prospectively followed. Serum was obtained during the first 10 hours postfracture and presurgery, 48–60 hours postop, 7 and 30 days postop, measuring CRP, interleukin-1 β (IL-1 β), IL-6, IL-8, tumor necrosis factor- α (TNF- α), IL-10, and IL-1 receptor antagonist (IL-1RA).

Results. A significant increase was found postop for CRP, IL-6, TNF- α , IL-1RA ($p < .001$), IL-10 ($p < .002$), and IL-8 ($p = .05$). CRP kinetics curves were higher in patients with complications as a group, and in those suffering from infections, delirium, and cardiovascular complications ($p < .05$). IL-6 increase in patients with complications approached significance. Additional complications appeared in patients with impaired mental status (IMS) versus cognitively normal patients ($p = .037$). Higher kinetics curves in the IMS patients were found for CRP and IL-6 ($p < .05$). Analyzing the interaction effect of complications and IMS on CRP and cytokines production demonstrated that the increase in CRP was independently related to complications and IMS. IL-6, IL-8, and IL-10 were higher in IMS patients but not in patients with complications without IMS ($p < .05$).

Conclusions. Serum CRP and cytokines increased drastically in postop hip-fracture elderly patients. Only CRP significantly and independently increased in IMS patients and in patients with complications, whereas cytokines significantly increased only in IMS patients. This study raises questions about possible effects that cytokine generation, after hip-fracture repair, might have on cognition and complications.

FRACTURE of the hip is one of the most common and potentially devastating injuries in the elderly population. Its incidence sharply increases in most areas of the world due to aging of the population and to age-related increase in fractures (1).

The elderly experience several changes in immune function, mainly in T-cell functioning. However, inconsistencies in age-associated cytokine production have been reported (2). Increased inflammatory activity reflected by high serum level of interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and C-reactive protein (CRP) have been widely studied (3,4). In addition, IL-6 has been implicated in the pathogenesis of several chronic diseases associated with aging, including osteoporosis, Alzheimer's disease, atherosclerosis, sarcopenia, and neoplasia and is tightly regulated and normally undetected in the serum of healthy young individuals unless compounded by trauma, infection, or other stress (5,6).

It has been suggested that an age-associated increase in IL-6 might explain the "chronic inflammation" appearance of some elderly individuals, even in the absence of an inflammatory focus (5). The role of inflammation in the pathogenesis of Alzheimer's disease is based on histopathological brain studies, circulating peripheral inflammatory

factors, and on the fact that certain anti-inflammatory drugs could modify the course of the disease (6,7). Senile plaques in Alzheimer's disease are associated with reactive astrocytes, activated microglial cells, overexpressing cytokines, and acute phase proteins (6). Several investigators reported increased blood levels of IL-1 β , IL-6, and antichymotrypsin in patients with Alzheimer's disease (8) and that gene polymorphism of IL-1 α , IL-1 β , and IL-6 are associated with an increased risk of the disease (9). The long-term prospective association between dementia (mainly Alzheimer's disease and vascular dementia) and CRP was demonstrated in men participating in the Honolulu–Asia Aging Study (10).

Very few studies have been reported on cytokines and CRP dynamics in hip-fracture-operated patients. Oka and colleagues (11) examined serum changes of IL-6 and CRP in elective nonorthopedic postoperative (postop) patients, concluding that circulating IL-6 is a valuable marker in early detection and prediction of postoperative complications. Conversely, Giannoudis and colleagues (12) studied orthopedic blunt trauma victims, and concluded that early assessment of CRP and IL-6 was not beneficial in diagnosing sepsis and that their levels following trauma should be assessed with caution. Ellitsgaard and colleagues (13) studied 140 hip-fracture-operated patients and found high

serum CRP levels in postop bronchopneumonia and deep wound infections.

The study by White and colleagues (14) of elective total knee or hip replacements concluded that any upward trend in the CRP level after the third postop day may suggest infection. In a similar study, Wirtz and colleagues (15) measured IL-6 and CRP levels and found IL-6 to be a superior marker for the inflammatory phase after knee or hip replacement.

To the best of our knowledge, no previous study has investigated the major cytokines associated with inflammation (proinflammatory: IL-1 β , IL-6, IL-8, TNF- α ; antiinflammatory: IL-1 receptor antagonist (IL-1RA), IL-10) in elderly hip-fracture-operated patients. We chose these cytokines, which are the most studied in inflammation and in elderly persons, and dementia (6).

Our objectives were to determine the kinetics of serum proinflammatory and antiinflammatory cytokines and CRP in elderly hip-fracture-operated patients over a month after fracture, to determine the relationship between these cytokines and postop complications and 6-month postop mortality, and to compare the kinetics of these cytokines and CRP in patients stratified by the Mini-Mental State Examination (MMSE) score (16).

METHODS

Patients and Setting

All elderly patients operated on for hip fracture between June 2001 and January 2002 in the Department of Orthopedics Golda Campus, Rabin Medical Center, were included in the study. Exclusion criteria were: age ≤ 65 years, multitrauma cases such as vehicle accidents, death expected within several days or weeks due to end-stage disease, and patients suffering from infections or chronic inflammatory conditions, those on antiinflammatory drugs, and those hospitalized after more than 10 hours postfracture. Data collected on admission included age, sex, chronic medical conditions, medications, type of fracture, and pre-hospital functional status. Follow-up data included length of stay, mortality due to complications, and functional outcome. All complications were confirmed by clinical, bacteriological, sonographic, and radiological parameters. Delirium was diagnosed using the Confusion Assessment Method (CAM) algorithm (17). Cardiovascular complications included cardiac ischemia or infarction and arrhythmia. After stabilization, most patients were transferred from the department to a rehabilitation hospital, while the remainder were sent home or to a nursing home.

Measurements and Laboratory Data

A multidisciplinary team headed by a geriatrician and consisting of a geriatric nurse, occupational therapist, and physical therapist performed a cognitive and functional comprehensive geriatric assessment. The diagnosis of dementia was based on the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) (18), requiring multiple cognitive deficits including memory impairment

and other cognitive disturbances and significant social or functional decline from a previous level of functioning. The team discussed each patient weekly, taking into account patient medical history, MMSE scores (16), functional and social preop status and patient functioning, and attitude and conduct during rehabilitation to classify the patient as demented or not. The MMSE (16) was performed by the geriatrician or by the occupational therapist and was used to determine cognitive level. Each patient was assessed on Day 1 of hospitalization, then reassessed after stabilization and during rehabilitation with the higher score being recorded. Patients were classified into two cognitive groups: impaired mental status (IMS) (score ≤ 23) and normal (24–30 points). Dementia was defined according to criteria detailed in the DSM-IV (18). The multidisciplinary team performed a comprehensive geriatric assessment and discussed each patient weekly to ascertain functional and mental status.

The Katz Index of Activities of Daily Living (ADL) (19) was used to categorize the patients into 3 prefracture functional groups: independent, partially dependent, and fully dependent according to a score of 10–12, 6–9, and 0–5 points out of 12, respectively. The scale has 6 items (bathing, dressing, toilet use, feeding, bed-to-chair transfer, and walking). The American Society of Anesthesiologists (ASA grading) system was used to measure the severity of patients' health problems at admission (20). We combined these grades into two categories: grades I + II and grades III + IV.

Following the Helsinki Committee's approval and informed written consent given by the patient or proxy, venous blood samples were obtained four times, to measure CRP, IL-1 β , IL-6, IL-8, TNF- α , IL-10, and IL-1RA, during the first 10 hours postfracture and presurgery, at 48–60 hours, and at 7 and 30 days postop, respectively. CRP was measured by nephelometric assay on an Array 360 Protein System (Beckman Coulter, Fullerton, CA) and was expressed in milligrams per deciliter (mg/dL). Serum levels of cytokines were measured by solid-phase enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN). This assay uses the quantitative "sandwich" enzyme immunoassay technique. Determination of IL-1 β and TNF- α was performed using high sensitivity immunoassay kits (Quantikine HS; R&D Systems) as described previously (21,22). Cytokine levels are expressed in picograms per milliliter, and in Log of their values in picograms per milliliter. The minimal detection levels of the cytokine assays (in picograms per milliliter) are: IL-1 β = 0.05, IL-6 = 5, IL-8 = 4, TNF- α = 4, IL-10 = 3.2, IL-1RA = 22.

Statistical Analysis

An analysis of variance (ANOVA) test with repeated measures was performed to determine within-patient effects of time (four measurements) and between-patient effects (complications [patients with complications vs patients without complications], cognitive groups, ASA grading, type of operation, aspirin use, and cardiovascular and cerebrovascular diseases) of CRP and of Log cytokines. Continuous variables (i.e., IL-6) were compared using the two-tailed Student *t* test. Categorical variables (i.e., complications) were compared by the chi-square test (or Fisher's

exact test). The Pearson correlation test was used to assess the relationship between continuous variables. Results are expressed as mean \pm standard error of the mean (*SEM*).

RESULTS

Ninety-four hip-fracture elderly patients were hospitalized during the study period. Seventeen were excluded because of their arrival more than 10 hours postfracture. Of the remaining 77 patients, only 41 were willing to participate in the study and were not excluded by the exclusion criteria. Their mean age was 81.8 ± 7.7 years, range 68–97 years. Only three were prefracture nursing home patients. Gender, mental status, prefracture functioning, fracture type, chronic medical conditions, ASA grading, and complications are summarized in Table 1. After surgery, 1 patient died in the Orthopedics Department, 2 went home, 1 returned to his nursing home, and the other 37 patients were transferred to a rehabilitation facility. After a 6-month follow-up, 7 (17%) patients had died. Mean levels of CRP and cytokines in the four time periods are detailed in Table 2.

Relationship Between CRP and Cytokine Levels and Complications

As a group, significant within-patient effects of the four time periods were found for CRP, IL-6, TNF- α , IL-1RA ($p < .001$), IL-10 ($p < .002$), and IL-8 ($p = .05$), but not IL-1 β ($p = 0.3$). Nineteen patients experienced 29 complications (Table 1). CRP and cytokine levels were compared in patients with and without complications. Different kinetics curves were found for only CRP ($p = .004$, Figure 1) and IL-6 ($p = .06$). A separate comparison of each complication's patient group, with the group of patients without any complications, showed different kinetics curves for CRP and infections ($p = .03$); CRP, IL-6, and cardiovascular complications ($p < .001$ and $p = .02$, respectively); and CRP, IL-8, and delirium ($p = .008$ and $p = .08$, respectively).

There were significantly more complications in IMS patients (9/12) compared to the cognitively normal patients (10/29) ($p = .037$). However, there was no correlation between age and complications.

Relationship Between CRP, Cytokine Levels to Cognition, Age, ASA Grading, Type of Operation, Cardiovascular Diseases, and Survival

Significantly higher kinetics curves in the IMS patients compared to the cognitively normal patients were found for CRP and IL-6 ($p < .001$), IL-8 ($p = .003$), and IL-10 ($p = .006$) (Figure 2); borderline significance was found for IL-1RA ($p = .076$) but not for IL-1 β and TNF- α ($p > .2$) (Table 3). The mean presurgery IL-1RA value was higher in the IMS patients than in the cognitively normal patients ($p = .04$).

No correlation was found between CRP, cytokine production, and age. In addition, no significant differences were found when comparing kinetics of CRP and cytokines in ASA Grades I+II versus Grades III+IV, type of operation (nailing vs hemiarthroplasty), use of aspirin (yes or no), cardiovascular and cerebrovascular diseases, or between patients who died or survived during the 6 months after the operation.

Table 1. Chronic Medical Conditions, ASA Grading, and Complications

Variables	Patients	
	No.	%
Gender		
Men	12	29
Women	29	71
Mental status		
Normal	29	71
Impaired mental status	12	29
Prefracture functioning		
Independent	10	24
Partially dependent	38	68
Fully dependent	3	7
Fracture type		
Intertrochanteric	27	65.8
Intracapsular	13	31.7
Subtrochanteric	1	2.5
Chronic medical conditions		
Hypertension	24	59
Gastrointestinal disease	12	29
Ischemic heart disease	11	27
Diabetes	9	22
Cerebrovascular accident	8	20
Genitourinary disease	7	17
Congestive heart failure	5	12
Cardiac arrhythmia	5	12
COPD	5	12
Chronic renal failure	5	12
Other	16	39
ASA grading		
Grades I + II	29	71
Grades III + IV	12	29
Complications		
Infections (pneumonia, UTI, sepsis)	8	20
Delirium	11	27
Cardiovascular	8	20
Cerebrovascular accident	2	5

Note: ASA = American Society of Anesthesiologists; COPD = chronic obstructive pulmonary disease; UTI = urinary tract infection.

Interaction Between Cognition and Complications in CRP and Cytokine Production

As CRP and some cytokines had higher kinetic curves both in patients suffering from complications and in IMS patients, we simultaneously analyzed the within-patient effects of each variable (complications or IMS) on CRP and cytokine production and investigated any possible interaction. We found that the increase in CRP was independently due to both complications and IMS ($p = .005$ and $p = .001$, respectively), and the interactions approached statistical significance ($p = .06$). In short, IMS patients with complications had a higher CRP than did IMS patients without complications. IL-6, IL-8, and IL-10 showed a significantly higher increase only in the IMS patients, not in patients with complications without IMS. No interactions were found between IMS and complications. Higher cytokine levels in the IMS patients, compared to those in the normal patients,

Table 2. Mean Values of CRP and Cytokines at the Four Time Periods

Variables	Preop (40)* (Mean \pm SEM)	48–60 h Postop (41)* (Mean \pm SEM)	7 d Postop (38)* (Mean \pm SEM)	30 d Postop (38)* (Mean \pm SEM)
CRP, mg/dL	1.51 \pm 0.44	17.06 \pm 1.12	7.34 \pm 1.03	3.34 \pm 0.88
IL-1 β , pg/mL	0.79 \pm 0.12	0.74 \pm 0.11	0.72 \pm 0.1	0.58 \pm 0.09
IL-6, pg/mL	39.44 \pm 4.67	47.27 \pm 5.45	20.84 \pm 3.29	14.67 \pm 2.80
IL-8, pg/mL	26.88 \pm 1.84	32.96 \pm 2.82	34.39 \pm 2.87	32.63 \pm 3.86
TNF- α , pg/mL	10.42 \pm 1.14	12.70 \pm 1.16	10.47 \pm 1.16	18.89 \pm 2.64
IL-10, pg/mL	7.18 \pm 1.20	6.40 \pm 0.89	4.22 \pm 0.34	4.35 \pm 0.47
IL-1RA, pg/mL	1019.6 \pm 103.7	2151.5 \pm 227.2	2259.9 \pm 251.1	1442.2 \pm 195.8

Notes: *The numbers in parenthesis are the numbers of patients whose serum samples were analyzed.

CRP = C-reactive protein; Preop = preoperative; Postop = postoperative; SEM = standard error of the mean; IL = interleukin; TNF- α = tumor necrosis factor- α ; IL-1RA = interleukin-1 receptor antagonist.

were related to the lower cognitive state, independent of the complications ($p = .003$, $p = .01$, and $p = .04$, respectively).

DISCUSSION

Surgical injuries induce alterations in hemodynamic, metabolic, and immune responses largely orchestrated by cytokines (23). In the present study we found: (a) a significant and weeks-lasting increase in proinflammatory and anti-inflammatory cytokines following hip-fracture repair; (b) that only CRP increases significantly in patients with complications, whereas IL-6 increases approach significance (this trend vanishes when cognition is taken into account); and (c) higher CRP, IL-6, IL-8, and IL-10 serum levels in the IMS patients compared to cognitively normal patients, independent of complications.

Previous studies have demonstrated that CRP is a sensitive parameter in monitoring orthopedic postop complications (13,14). However, conflicting data exist regarding the value of IL-6 in monitoring orthopedic postop complications (12,15). The present study demonstrates that CRP is superior to IL-6 in monitoring postop complications as a group and in monitoring infectious, delirious, and cardiovascular complications individually. In fact, we found that the CRP

higher kinetic curve was independently due to both complications and IMS, with interactions approaching statistical significance. Although IL-6 is the chief stimulator of CRP, other cytokines are capable of stimulating the production of acute-phase proteins (24). Thus, a CRP increase may not necessarily be exactly parallel to an IL-6 increase. Furthermore, IL-6 secretion by peripheral blood mononuclear cells was found to increase in patients with Alzheimer's disease (25), thus its production in postop demented patients with complications might be altered and somewhat different from that of CRP production.

A substantial number of patients had complications. This finding can be explained by the advanced age of the patients, the high rate of IMS and dependent patients, and also by the fact that we included delirious cases, usually excluded by other authors. We diagnosed delirium in 27% of our patients, yet, delirium can affect up to 65% of elderly patients after hip-fracture repair (26). From a clinical point of view, following elderly patients after hip-fracture surgical repair and measuring CRP (but not cytokines) 48–72 hours postop can be useful in detecting and treating complications. It is important to remember that the increase in CRP is independently seen in patients with complications and in those with IMS, whereas IL-6, IL-8, and IL-10 only increase in IMS patients but not in patients with complications without IMS.

Contrary to all cytokine kinetics, we did not find a significant within-patient effect of the four time periods for IL-1 β , probably due to its early production after acute injury and immediate release long before the patient's arrival to the hospital and because it is presynthesized and ready to serve as an immediate source of cytokine (27). IL-6, in comparison, is detectable in 60 minutes and peaks between 4 and 6 hours after injury. Effectively, IL-1 β values in the first three serum samples were similarly elevated, decreasing in the fourth sample obtained several weeks later. Consistent with this concept is the significant difference in IL-1RA values over the four time periods, indicating the dynamic feedback of this receptor antagonist to the increase in IL-1 β . IL-1RA is often used as a surrogate marker of IL-1 effects, exhibiting a dose-response inhibition of IL-1 effects.

The literature has been contradictory regarding peripheral cytokine dysregulation in Alzheimer's disease (28). Some studies have demonstrated increased serum levels of IL-1 β , IL-6, and TNF- α (25,29), whereas others did not (30,31). In

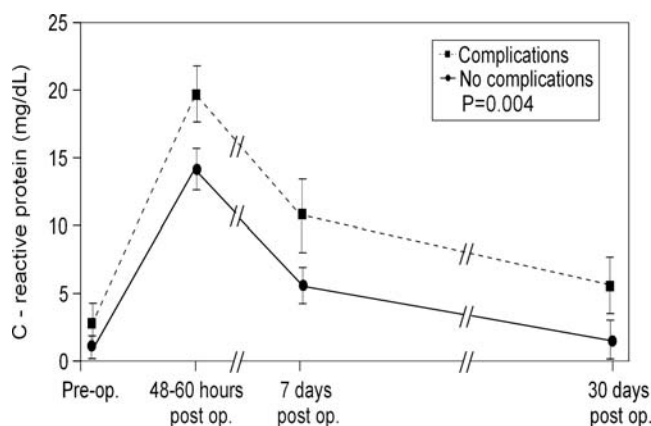


Figure 1. C-reactive protein (CRP) kinetics curves in hip-fracture-operated patients with complications, compared to patients without complications. Pre-op = preoperative; post op. = postoperative.

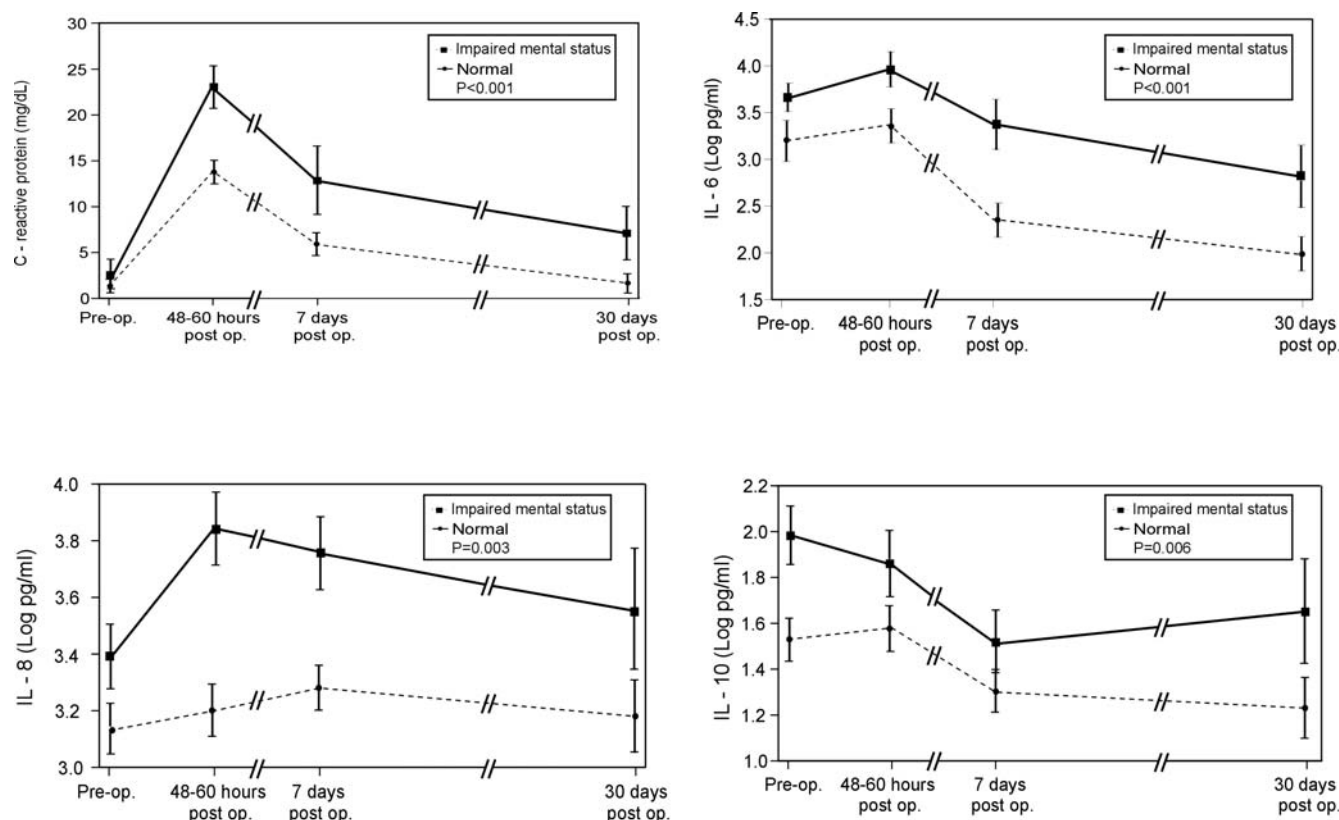


Figure 2. C-reactive protein (CRP) and cytokine kinetics curves in hip-fracture-operated IMS patients, compared to cognitively normal patients. Pre-op. = preoperative; post op. = postoperative.

vascular dementia, even higher serum proinflammatory cytokines (IL-1 β , TNF- α) were found compared to mild-to-moderate Alzheimer's disease (32). Other studies showed similar serum levels of IL-1 β in patients with Alzheimer's disease, multiinfarct dementia, and controls (33) and a marked reduction of serum TNF- α in Alzheimer's disease and multiinfarct dementia compared to controls (33). The current study is in agreement with previous studies showing higher proinflammatory and antiinflammatory cytokines in demented patients. Whether such cytokine levels represent "spillover" from central nervous system inflammatory processes or an influence of peripheral cytokine dysregulation on cognitive processing remains to be determined (8,28).

Stress increases cytokine production, which plays an important role in mediating activation of central neurotransmitters and the sympathetic nervous system (28). Physical or psychological stress increased IL-6 and IL-1 β concentration (34), and in animal models, acute stress induced IL-1 β expression in various brain regions (35). Brain IL-1 β administration produced a similar effect to those produced by stressors, including increased plasma adrenocorticotrophic hormone (ACTH) and glucocorticoid levels (36). Lipopolysaccharides (LPS) stimulate macrophages to produce IL-1 β , IL-6, and TNF- α . Thus, peripheral cytokines most likely mediate LPS-induced effects (37) including the "sickness behavior" syndrome, characterized by fever,

anorexia, reduced mobility, disordered sleep, and cognitive impairment (38). The activation of cytokine production coupled with central neurotransmitters and hormonal increase, secondary to stress, was found to be associated with impaired immune function and infections (39,40).

Combining the cytokine effect on the immune system and cognition, and taking into account the higher CRP, cytokine levels, and complication rates in the demented patients, we wonder whether the "cytokine storm" demonstrated in this study can further intervene in the high complication rate in hip-fracture-operated patients.

One limitation of our study was the small number of patients. However, because our patients were not selected and all hip-fractured elderly persons fulfilling the inclusion criteria during a given period of time were included, this limitation is almost negligible. These patients represent the aging population, characterized by a substantial number of chronic diseases, functional decline, and cognitive impairment. Another limitation is the analysis of heterogenic demented patients as a whole, lacking separate analysis for Alzheimer's and vascular dementia. However, as we demonstrated above, cytokine production is probably similar in both types of dementia. Moreover, the small number of patients would have rendered separate analysis impossible. Finally, even from a practical and clinical point of view, not all of the cases of dementia can be accurately categorized, especially in this old and frail population.

Table 3. Mean Levels of CRP and Cytokines at the Four Time Periods, in Impaired Mental Status and in Cognitively Normal Patients

Variables	Preop (Mean \pm SEM)	48–60 Hours Postop (Mean \pm SEM)	7 Days Postop (Mean \pm SEM)	30 Days Postop (Mean \pm SEM)
CRP, mg/dL				
Normal	1.28 \pm 0.5	13.85 \pm 1.1	5.87 \pm 0.9	1.66 \pm 0.8
IMS	2.46 \pm 1.2	23.32 \pm 2.0	12.77 \pm 3.4	7.07 \pm 2.3
IL-1 β , pg/mL				
Normal	0.61 \pm 0.1	0.65 \pm 0.11	0.74 \pm 0.12	0.56 \pm 0.12
IMS	1.21 \pm 0.32	0.94 \pm 0.25	0.65 \pm 0.18	0.63 \pm 0.12
IL-6, pg/mL				
Normal	35.90 \pm 5.41	38.46 \pm 5.54	13.25 \pm 2.16	9.43 \pm 1.61
IMS	47.68 \pm 9.00	68.59 \pm 11.02	40.85 \pm 8.01	27.52 \pm 7.78
IL-8, pg/mL				
Normal	25.22 \pm 2.05	26.68 \pm 1.98	29.64 \pm 2.50	27.77 \pm 2.89
IMS	30.78 \pm 3.72	48.14 \pm 6.72	46.90 \pm 6.95	44.55 \pm 10.80
TNF- α , pg/mL				
Normal	9.96 \pm 1.19	12.12 \pm 1.02	9.87 \pm 1.39	18.96 \pm 3.31
IMS	11.49 \pm 2.63	14.12 \pm 3.16	12.03 \pm 2.07	18.70 \pm 4.34
IL-10, pg/mL				
Normal	5.55 \pm 0.63	5.64 \pm 0.72	3.87 \pm 0.29	3.48 \pm 0.12
IMS	11.00 \pm 3.60	8.23 \pm 2.52	5.15 \pm 0.93	6.49 \pm 1.47
IL-1RA, pg/mL				
Normal	890.3 \pm 117.3	1973.3 \pm 239.9	2199.4 \pm 318.5	1244.3 \pm 212.1
IMS	1321.5 \pm 190.7	2582.2 \pm 512.7	2419 \pm 374.8	1928.0 \pm 411.0

Note: Preop = preoperative; Postop = postoperative; SEM = standard error of the mean; CRP = C-reactive protein; IMS = impaired mental status; IL = interleukin; TNF- α = tumor necrosis factor- α ; IL-1RA = interleukin-1 receptor antagonist.

Conclusion

The results of the present study demonstrate a significant increase in serum CRP and proinflammatory and anti-inflammatory cytokines in postop hip-fractured elderly patients. After hip surgery, only CRP significantly and independently increased more in IMS patients and in patients with complications, whereas the cytokines significantly increased only in the IMS patients. This study raises questions concerning some possible effects that cytokine generation, post hip-fracture repair, might have on cognition and complications.

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