

Immunological Status of Elderly Patients Eligible for Arthroplasty after a Femoral Neck Fracture: Relationship between the Patients' Status, their Age and Postoperative Morbimortality*

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Purpose. To analyze the relationship between a patient's immunological status prior to arthroplasty secondary to a femoral neck fracture and postoperative complications.

Materials and methods. Prospective randomized study of 94 patients (81 of which female) with a Garden IV femoral neck fracture (mean age: 82.9 years (\pm 7.48), range: 100-64). On admission, the following parameters were evaluated in the patients' peripheral venous blood: differential leukocyte count; immunoglobulin (IgG, IgA, IgM and IgE); percentage of CD19, CD3, CD4 and CD8; transferrin levels; alfa-2-macroglobulin; ceruloplasmin; retinol transport protein; prealbumin; albumin; total proteins; total cholesterol and triglycerides. Postoperative complications were studied. Statistics: Variance and chi square analysis.

Results. There were twelve cases of surgical wound infection, 27 of urinary infection, 3 cases of pneumonia and one periprosthetic infection. Patients with a postoperative infection had lower preop levels of IgM (urinary infection and pneumonia), IgA (pneumonia) and IgE (wound infection), as well as a lower count of CD4 and CD8 per cubic mm (urinary infection and pneumonia) and a lower percentage of CD19 (wound infection). Albumin, prealbumin, total cholesterol, triglycerides and transferrin decreased significantly with age.

Conclusions. The IgM, IgA, IgE, the CD19 percentage and CD4 and CD8 counts could be used indicators of a higher risk of developing infections after surgery for a femoral neck fracture.

Key words: hip fracture, elderly patient, immunological response.

Estado inmunológico de ancianos candidatos a artroplastia tras fractura subcapital de cadera: estudio de su relación con la edad y con la morbilidad postoperatoria

Objetivo. Analizar la relación de la situación inmunológica preoperatoria tras fractura subcapital de cadera con las complicaciones postoperatorias.

Material y método. Estudio prospectivo aleatorio de 94 pacientes (81 mujeres) con fractura subcapital de cadera Garden IV (edad media: 82,9 años (\pm 7,48), máximo: 100, mínimo: 64 años). Al ingreso se determinó en sangre venosa periférica: fórmula leucocitaria, inmunoglobulinas (IgG, IgA, IgM e IgE), CD19, CD3, CD4, CD8, niveles de transferrina, alfa-2-macroglobulina, ceruloplasmina, proteína transportadora de retinol, prealbúmina, albúmina, proteínas totales, colesterol total y triglicéridos. Se estudiaron las complicaciones postoperatorias. En la estadística se realizó análisis de la varianza y Chi cuadrado.

Resultados. Se detectaron 12 casos de infección de la herida quirúrgica, 27 casos de infección de orina, 3 casos de neumonía y una infección periprotésica. Los pacientes con infección postoperatoria presentaron en el preoperatorio menores niveles de IgM (infección de orina y neumonía), de IgA (neumonía) y de IgE (infección de la herida), menor número de CD4 y CD8/mm³ (infección de orina y neumonía) y un menor porcentaje de CD19 (infección de herida). La albúmina, la prealbúmina, el colesterol total, los triglicéridos y la transferrina disminuyeron significativamente con la edad.

Conclusiones. La IgM, la IgA, la IgE, el porcentaje de CD19 y el número de CD4 y CD8 podrían servir como indi-

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cadres de un mayor riesgo de desarrollar infecciones durante el postoperatorio de una fractura subcapital de cadera.

Palabras clave: *fractura de cadera, anciano, respuesta inmunológica.*

MATERIALS AND METHODS

Patients, surgery and perioperative treatment

Ninety-four individuals (81 women) were randomly selected among those patients admitted to our hospital for a displaced subcapital hip fracture (Garden type IV), who were eligible to an arthroplasty (25 cases of cemented THR with an Exeter stem, and the rest a cemented Thompson-type hemiarthroplasty). None of the patients had a history of immunological, neoplastic or parasitic disease; none of them had undergone surgery in the 6 months prior to this study. Mean age was 82.9 years (± 7.48), with a maximum of 100 and a minimum of 64. A record was made of surgery time, the type of arthroplasty implanted and the number of red blood cell concentrates transfused. On admission, antithrombotic prophylaxis was begun with low molecular weight heparin every 24 hours. Half an hour before surgery, antibiotic prophylaxis was administered in the form of 1 g of IV cephazolin, maintaining perfusion for 24 hours, at a rate of 1 g every 8 hours. In patients allergic to penicillin, cephazolin was replaced by 600 mg clindamycin half an hour before surgery, plus 600 mg IV every 8 hours for 24 hours. In the first 48 hours, an IV analgesic perfusion of 2 g metamizole was administered every 6 hours. The study was approved by the Ethics Committee of our hospital.

Blood tests

A series of fasting peripheral venous blood samples were collected on admission, which were used to determine:

1) Immunological variables: white blood cell count and leukocyte formula, immunoglobulins (IgG, IgA, IgM and IgE) (determined by nephelometry), percentage of B (CD 19) and T (CD 3) lymphocytes (by means of flow cytometry and monoclonal antibodies), and T lymphocyte subpopulations (CD4 and CD8).

2) Nutritional variables: transferrin, alfa-2-macroglobulin, ceruloplasmin, retinol binding protein, prealbumin, albumin, total protein, total cholesterol and triglycerides.

Morbidity study

A study was carried out of postoperative complications, healing time of the surgical wound, hospitalization time and the appearance of post-op complications; a mortality analysis was performed. Altmeier's (1979) criteria were used in or-

der to identify a surgical wound as infected. Urine was considered infected when the presence of clinical symptoms (fever, leukocytosis and dysuria) was compounded by a urine culture positive to a germ of which at least 100,000 colony-forming units were found. Postoperative pneumonia was assessed on the basis of the clinical data, the x-ray report and the existence of a positive bronchial or blood culture.

Statistical analysis

A descriptive statistical analysis was carried out of each one of the variables under study. The Analysis of Variance (ANOVA), together with the Bonferroni correction, was used to study the relationship between quantitative and qualitative variables. The chi square test was used to compare two qualitative variables (together with Fisher's Exact Test when appropriate). Data with $p < 0.05$ were considered statistically significant.

RESULTS

Six women (79-99 years) died during their hospitalization: three strokes, one brain hemorrhage, one case of pulmonary embolism and two cases of heart failure. The mortality rates per decades were as follows: 61-70 years, 0%; 71-80 years, 4.76%, 81-90 years 6.25%; 91-100 years, 16.6%. Twelve instances of surgical wound infection were detected, as well as 27 cases of urine infection, 3 cases of pneumonia and one periprosthetic infection, which required explantation of the arthroplasty.

Table 1 summarizes the differences detected in the variables studied preoperatively in the peripheral blood, in comparison with postoperative infections. The 82-year old patient who developed a periprosthetic infection presented with pre-op measurements for IgG (654 mg/dl), IgM (43.4 mg/dl), CD3 ratio (63%) and CD8 ratio (20%) that were lower than the reference values established by our Hospital's laboratory. We found no relation between diabetes (6 patients with insulin-dependent diabetes mellitus, 8 patients with non-insulin-dependent diabetes mellitus) and infection.

With respect to age, the percentage of basophils fell significantly as a function of age (fig. 1); the CD19 ratio (B cells) dropped between 60 and 90 years and increased during the ninth decade (fig. 2), and the CD4 ratio (cooperating T-lymphocytes) (fig. 3), together with the amount of CD4/mm³ (fig. 4), fell with age. The CD8 ratio (cytotoxic/suppressor T lymphocytes) (fig. 5) increased with age.

We can observe an age-related increase of IgA e IgE that is nevertheless not statistically significant. Albumin, prealbumin, total cholesterol, triglycerides and transferrin levels dropped considerably with age (table 2), whereas the other nutritional variables did not show any significant differences.

Table 1. Differences detected in the variables studied preoperatively in the peripheral blood, as compared with postoperative infections

	Pneumonia		Wound infection		Urinary infection	
	Yes ± SE	No ± SE	Yes ± SE	No ± EE	Yes ± SE	No ± EE
Percentage of lymphocytes	6.3 ± 1.9	10.3 ± 0.7	7.7 ± 0.8	10.7 ± 0.8		
IgA mg/dl	234.6 ± 11.9	299.1 ± 15.6				
IgM mg/dl	77.3 ± 25.9	109.9 ± 13.8			88.2 ± 8.9	119.1 ± 19.6
IgE UI/ml	96.1 ± 22.5	133.7 ± 35	94.1 ± 49.1	136.9 ± 37.9		
CD4/mm ³	295.9 ± 38.8	608.7 ± 42.5			548.7 ± 68.9	611.5 ± 52.6
CD8/mm ³	138.6 ± 9.5	424.2 ± 130.4			237.7 ± 31.1	492.7 ± 188.6
CD19 ratio	9.9 ± 1.3	12.7 ± 0.7				

SE: standard error; IgA: immunoglobulin A; IgE: immunoglobulin E; IgM: immunoglobulin M.

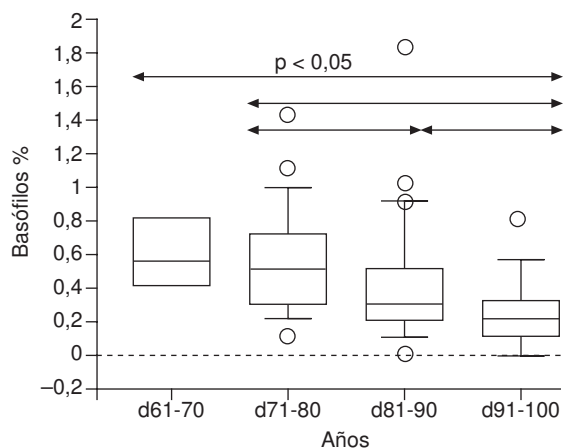


Figure 1. Percentage of basophils in the different decades of life. d: decade.

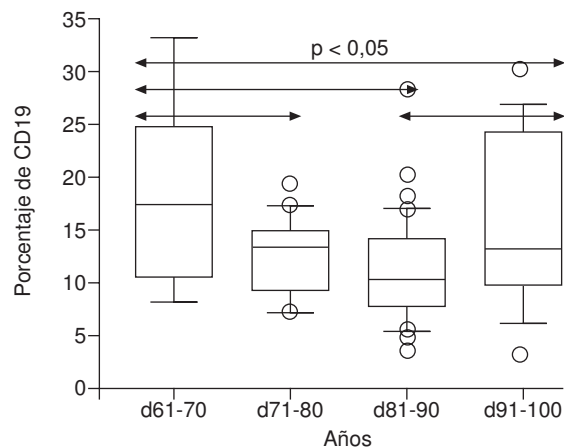


Figure 2. CD19 ratio in the different decades of life. d: decade.

DISCUSSION

The patients' immunological response to surgical stress and to infection vary with age²⁻⁵. Several immunological alterations have been described in elderly persons, among them a dysfunction of phagocytic activity of polymorph nucleocytes (PMNs) and macrophages, and lower proliferation levels of T-lymphocytes further to their *in vitro* stimulation by mitogens. The most frequently-used immunological test to measure the immunological response in the elderly and in surgical patients is the Delayed Hypersensitivity Skin Test. From age 70, subjects progressively lose their capacity to react to the intradermal application of an antigen with which the subject had had no previous contact⁶. However, with the advent of modern lab techniques to our hospitals (flow cytometry, enzyme-immune assays and monoclonal antibodies), skin tests – often uncomfortable for the patient and difficult to assess – can be replaced by other ways of more accurately revealing the immunological status of an elderly patient that is due to undergo surgery.

In our study, we found an age-related fall in the percentage of B lymphocytes and in both the CD4 ratio and CD4 count. This finding, together with the fact that the pa-

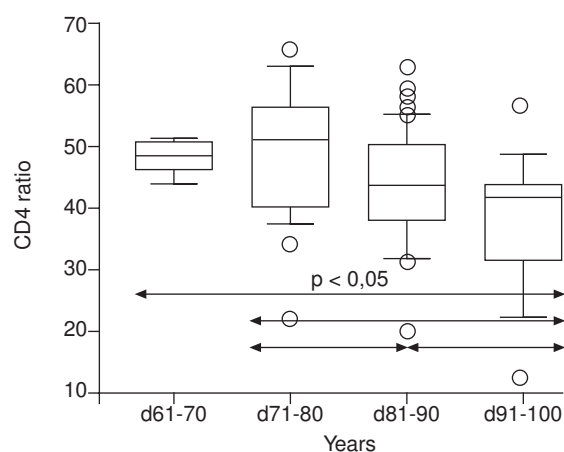


Figure 3. CD4 ratio in the different decades of life. d: decade.

tients in our series who developed a postoperative infection preoperatively had lower levels of IgM (in cases of urine infection and pneumonia), IgA (in cases of pneumonia) and IgE (in cases of wound infection), and fewer CD4s and CD8s/mm³ (in cases of both urine infection and pneumonia), as well as a lower percentage of total lymphocytes (in

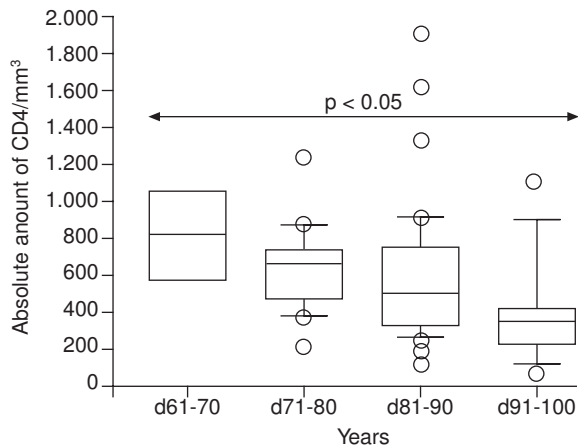


Figure 4. CD4/mm³ in the different decades of life. d: decade.

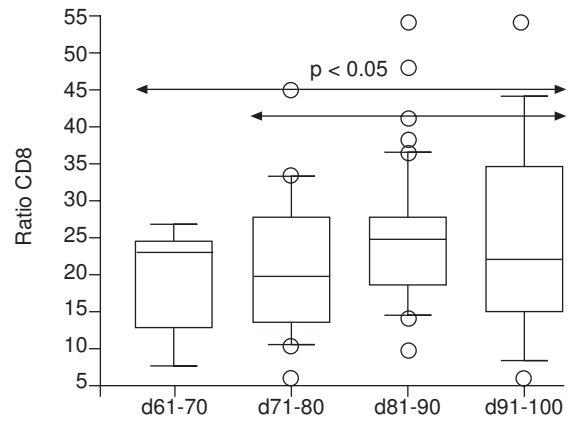


Figure 5. CD8 ratio in the different decades of life. d: decade.

Table 2. Nutritional variables studied in the peripheral blood with significant age-related changes (p < 0.05) (standard error)

mg/dl	61-70 years	71-80 years	81-90 years	91-100 years
Albumin	3.66 ± 0.16	3.34 ± 0.8	3.16 ± 0.65	3.1 ± 0.11
Prealbumin	15.8 ± 0.96	15.2 ± 1.03	12.6 ± 0.6	9.6 ± 0.86
Total cholesterol	214.2 ± 23.9	179.7 ± 6.8	164.7 ± 4.9	135.6 ± 10.4
Triglycerides	186.7 ± 65.9	109.9 ± 9	98.8 ± 7.2	66.7 ± 12.8
Transferrin	182 ± 22.5	176.9 ± 5.7	167.1 ± 4.9	152.7 ± 7.9

cases of wound infection and pneumonia), would explain the increase in the incidence of infection as patients get older. In fact, CD4s play a role in recognizing the antigen in association with the molecules of the type-II7 human leukocyte antigen. CD4s Th-1 cells also play a key role in activating PMNs, in the proliferation and differentiation of T cells and they are responsible for the delayed hypersensitivity phenomenon⁸. CD4 Th-2 cells are also key since they stimulate the B(lymphocyte precursor cell. CD8 is considered the main culprit behind the death and removal of extraneous cells. Activated T lymphocytes (CD8s), in addition to being cytotoxic cells, also give rise to a subpopulation of suppressor cells that regulate immunological function⁹.

Nonetheless, in spite of having detected an age-related decrease in the levels of some nutritional variables (albumin, prealbumin, total cholesterol, triglycerides and transferrin), these did not seem to be related to the appearance of postoperative infection. Marín et al¹⁰ found a correlation between the preoperative lymphocyte count on the one hand, and delayed healing and infection of the surgical wound on the other in patients subjected to hip or knee replacement; in that paper, however, albumin and transferrin did not appear to be related to wound healing, although there were decreased albumin levels in the majority of patients that developed a surgical infection.

As regards the causes of mortality in our series, they are in line with those described by Lie et al¹¹, where vascular conditions are the most frequent. In addition, the proportion of women in our study is similar to that in Serra et al¹².

To conclude, we believe that IgE and the CD19 ratio could indicate a higher risk to develop a postoperative wound infection. IgM, IgA and the CD4 and CD8 count could constitute a prognostic factor for a higher risk of developing pneumonia; these same variables, with the exception of IgA, are associated with a post-op urine infection further to a hip fracture. The percentage of total lymphocytes is lower in the preoperative study of patients that postoperatively develop wound infection or pneumonia. We can use this simple and objective system to detect patients at a higher risk of experiencing these complications.

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Conflict of interests

The authors have declared that they have no competing interests.