Amino Acids (2006) 31: 463–469
DOI 10.1007/s00726-005-0287-5

Amino Acids
Printed in Austria

The relationship between albumin, other plasma proteins and variables, and age in the acute phase response after liver resection in man

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Received September 29, 2005
Accepted October 27, 2005
Published online April 4, 2006;

Summary. A large series of plasma albumin (ALB, g/dl) and simultaneous blood and clinical measurements were prospectively performed on 92 liver resection patients, and processed to assess the correlations between ALB, other plasma proteins, additional variables and clinical events. The measurements were performed preoperatively and at postoperative day 1, 3 and 7 in all patients, and subsequently only in those who developed complications or died. In patients who recovered normally ALB was 4.3 ± 0.4 g/dl (mean $\pm$ SD) preoperatively, 3.7 ± 0.7 at day 1 and 3, and 3.9 ± 0.4 at day 7. In patients with complications its decrease was more prolonged. In non-survivors it was 3.4 ± 0.4 preoperatively, 3.0 ± 0.4 at day 1, and then decreased further. Regression analysis showed direct correlations between ALB and pseudo-cholinesterase (CHE, U/l, nv 5300-13000), cholesterol (CHOL, mg/dl), iron binding capacity (IBC, mg/dl), prothrombin activity (PA, % of standard reference) and fibrinogen, an inverse correlation with blood urea nitrogen (BUN, mg/dl) for any given creatinine level (CREAT, mg/dl), and weaker direct correlations with hematocrit, other variables and dose of exogenous albumin. An inverse relationship found between ALB and age (AGE, years) became postoperatively (POSTOP) also a function of outcome, showing larger age-related decreases in ALB associated with complications (COMPL: sepsis, liver insufficiency) or death (DEATH). Main overall correlations: $CHE = 287.4(2.014)^{ALB}$, $r = 0.73$; $CHOL = 16.5(1.610)^{ALB}\,(1.001)^{ALKPH}$, $r = 0.71$; $IBC = 68.6(1.391)^{ALB}$, $r = 0.64$; $PA = 13.8 + 16.0(ALB)$, $r = 0.51$; $BUN = 21.3 + 20.2(CREAT) - 6.2(ALB)$, $r = 0.91$; $ALB = 5.0\text{–}0.013(AGE) - \{0.5 + 0.003(AGE)_{COMPL} + 0.012(AGE)_{DEATH}\}_{POSTOP}$, $r = 0.74$ [$p < 0.001$ for each regression and each coefficient; ALKPH = alkaline phosphatase, U/l, nv 98-279, independent determinant of CHOL; discontinuous variables in italics label the change in regression slope or intercept associated with the corresponding condition]. These results suggest that altered albumin synthesis (or altered synthesis unable to compensate for albumin loss, catabolism or redistribution) is an important determinant of hypoalbuminemia after hepatectomy. The correlations with age and postoperative outcome support the concept that hypoalbuminemia is a marker of pathophysiologic frailty associated with increasing age, and amplified by the challenges of postoperative illness.

Keywords: Plasma albumin – Proteins – Pseudo-cholinesterase – Age – Liver resection – Acute phase response – Iron binding activity

Introduction

Hepatectomy is a singular operation in which an organ deeply involved in protein synthesis and acute phase response is partly resected, and subsequently undergoes rapid regeneration with a large need for amino acids to support parenchymal regeneration and acute phase synthetic processes (Milland et al., 1990; Tygstrup et al., 1996; Giovannini et al., 2004). Albumin is the most abundant extracellular protein (about 300 g in the healthy adult), is synthesized in the liver at a rate of 9 to 25 g/day, thus accounting for half of the total hepatic protein synthesis, and has a serum half-life of about 20 days (Rothschild et al., 1988; Camu et al., 1995; Marinella and Markert, 1998; Nicholson et al., 2000; Franch-Archas, 2001; Evans, 2002). Although it is perceived as the most important plasma protein (3.5–5.0 g/dl), it is distributed in larger amounts in extravascular space where it regulates the distribution of water among different tissues (Tullis, 1977a, b; Doweiko and Nompleggi, 1991a; Erstad et al., 1991; Gonzales and Kannewurf, 1998). Due to the higher intravascular concentration, albumin is responsible for 75–80% of osmotic pressure in plasma, the direct osmotic effect accounting for 60% of oncotic pressure, and the attractive force related to its strong negative charge, the Gibbs-Donnan effect, for the remainder (Nicholson et al., 2000). The full spectrum of its biologic actions is still not completely delineated. However it also includes the transport of many endogenous and exogenous ligands in the blood stream (ions, metals, hormones,

bilirubin, bile salts and pigments, amino acids, fatty acids, eicosanoids, nitric oxide, vitamins, drugs and other substances) (Anton, 1960; Masson, 1989; Doweiko and Nompleggi, 1991b; Stamler et al., 1992; Awad et al., 1999; Evans, 2002; Nicholson et al., 2000), a contribution to the acid-base balance, and a large series of protective effects through antioxidant and antiinflammatory properties, and influences on redox balance, capillary permeability, microvascular integrity, rheology of circulation, coagulation, cell signalling and apoptosis (Jorgensen and Stoffersen, 1979, 1980; Wayner et al., 1985; Halliwell, 1988; De Lorgeril et al., 1990; Doweiko and Nompleggi, 1991a, c; Wu et al., 1991; Keaney et al., 1993; Giovannini et al., 1993a; Kaufmann et al., 1995; Zoellner et al., 1996, 1999; Loban et al., 1997; Goldwasser and Feldman, 1997; Nicholson et al., 2000; Evans, 2002; Powers et al., 2002a, b; Vincent et al., 2003). This study has been performed to assess the pathophysiological and clinical correlates of changes in plasma albumin concentration (ALB, g/dl) after hepatectomy.

Materials and methods

Hepatectomies were performed in 92 patients (47 women, 45 men). The mean (±SD) age was 57 ± 12 years, body weight was 70 ± 11 kg, the ratio of actual to ideal body weight was 1.13 ± 0.16 (1983 Metropolitan Tables, 1984), body surface area 1.78 ± 0.15 m^2 (Du Bois and Du Bois, 1916), and body mass index (weight/height^2) was 25.0 ± 4.0 kg/m^2. Thirty-six patients had primary liver malignancy (23 with hepatocarcinoma, 10 with cholangiocarcinoma, 3 with other neoplasms), 35 had secondary hepatic malignancies (23 from colorectal cancer, 12 from other sources), and 21 had benign lesions. Eighteen patients had post-hepatitic Child-A liver cirrhosis. Fifty-four patients were in ASA class I (Djokovic and Hedley-Whyte, 1979), 7 in class II, 30 in class III, and 1 in class IV. All patients were in good nutritional condition; the actual/ideal body weight ratio was <0.9 in only 5 cases. Hepatectomies consisted of 43 minor (<3 liver segments) and 49 major resections (3–6 segments), all performed by the same surgeon (G.N.). The mean number of resected segments was 3 ± 1. There were 17 associated bowel operations (resections for primary malignancy or Roux-en-Y biliary reconstructions). The duration of the operations was 390 ± 149 min, that of normothermic ischemia of the liver 42 ± 27 min in 46 cases with continuous ischemia, and 57 ± 28 min in 19 cases with intermittent ischemia (Nuzzo et al., 2001). Seventy-one patients had normal postoperative recovery, whereas 15 had nonlethal complications: 9 had intraabdominal or pulmonary sepsis, 5 had transient liver insufficiency, and 1 had a biliary fistula without sepsis. The diagnosis of sepsis was based on previously described criteria involving the presence of a systemic septic response and positive cultures from blood or from the source of infection (Giovannini et al., 1993b). Patients with clinically relevant disseminated intravascular coagulation were excluded. Six patients died. The study was carried out prospectively except for the inclusion of three non-survivors observed outside the prospective period: this expanded the frame of reference for non-survivors without bias, as the pattern of death was similar in all cases (systemic sepsis with liver and/or respiratory insufficiency progressing to multiple organ failure or shock). The patient population provided a continuous distribution of observations, from minor to superextended hepatectomies, and from normal postoperative recovery to preterminal illness, which was suited to assessing the correlates of changes in ALB over a wide range of pathophysiologic abnormalities.

The data collected included 518 venous blood measurements. These were performed in accordance with the normal clinical routine for hepatectomies, without the need for specific consent, preoperatively and on postoperative days 1, 3 and 7 in all patients. Subsequently, measurements were continued only in patients with complications until recovery or death. The following continuous and discontinuous variables were considered: plasma ALB (g/dl), total protein (PROT, g/dl), fibrinogen (FIBR, mg/dl), total cholesterol (CHOL, mg/dl), triglycerides, glucose, urate, bilirubin, creatinine (CREAT, mg/dl), urea nitrogen (BUN, mg/dl), iron binding capacity (IBC, mg/dl, estimating transferrin levels) (Crosby et al., 1984), sodium, chloride, potassium, calcium (CA, mg/dl), magnesium, phosphate, and values of prothrombin activity (PA, % of standard reference), partial thromboplastin time, aspartate and alanine aminotransferase, alkaline phosphatase (ALKPH, U/l, nv 98-279), gamma-glutamyltranspeptidase, pseudo-cholinesterase (CHE, U/l, nv 5300-13000), lactic dehydrogenase, creatine-phosphokinase, hematocrit (HCT, %), hemoglobin concentration, blood cell counts, number of resected liver segments, duration of the operation, duration of intraoperative liver ischemia, intraoperative and perioperative transfusions, crystalloid and colloid infusions, length of postoperative hospital stay, presence of cirrhosis, neoplastic disease, previous chemotherapy, occurrence of associated bowel operations, sepsis and cholestasis. The APACHE II score (Knaus et al., 1985) in the first postoperative day was available in 59 patients. According to our protocol for hepatectomies, all patients received in the early postoperative period low-dose parenteral glucose (2.0 ± 1.4 g/kg/day), with amino acids (0.8 ± 0.6 g/kg/day, preferably 35 to 50% branched-chain) to support liver regeneration, up to postoperative day 3. Subsequently, parenteral regimen was continued only if oral feeding could not be resumed, and reached full-dose parenteral nutrition, including also fat (50% medium-chain and 50% long-chain triglycerides) in cases with prolonged illness. Exogenous albumin was administered intraoperatively as part of the anesthesiologic support, in the form of albumin solutions or fresh frozen plasma, for volume expansion or correction of acute coagulopathy. It was administered postoperatively to maintain plasma albumin above 2.5 g/dl, or 3.0 g/dl in patients with bilioenteric or enteric anastomoses, or liver cirrhosis. Statistical analysis was based on least square regressions, with analysis of residuals, skewness and kurtosis, 95% confidence limits of regression coefficients (Scheffé), and a "simplest best fit" program selecting the simplest possible regressions controlling the largest possible variability of albumin, based on Mallows' Cp criteria (Seber, 1977). This allowed us to assess the hierarchy of correlations and the main factors associated with the variability of ALB. Discriminant analysis was performed by using the Statgraphics package (Statgraphics Plus, Manugistics Inc., Rockville, USA).

Results

Plasma albumin decreased postoperatively in all cases. Mean ± SD preoperative and postoperative values are listed in Table 1, with a grouping based on patient outcome (normal recovery, occurrence of postoperative complications, or death). This showed a trend for an association between low preoperative or postoperative ALB and poor outcome. Regression analysis showed that, amongst all blood variables, the best correlates of ALB were CHE, CHOL, CA, IBC, PROT and PA (direct relationships, $r = 0.73$ to 0.51, $p < 0.001$ for all) (Table 2). Albumin was also directly related to FIBR ($r = 0.47$, $p < 0.001$), more weakly to HCT, lymphocyte, neutrophil and platelet

Table 1. Plasma albumin concentration (g/dl, mean ± SD) in different groups of patients at various postoperative days

	Preoperative	Day 1	Day 3	Day 7	Final[a]
Normal recovery	4.3 ± 0.4	3.7 ± 0.4	3.7 ± 0.4	3.9 ± 0.4	
Complications with survival	4.2 ± 0.4	3.7 ± 0.6	3.8 ± 0.5	3.7 ± 0.5	3.5 ± 0.5
Complications w/o survival	3.4 ± 0.4	3.0 ± 0.7	2.9 ± 0.5	3.1 ± 0.7	2.8 ± 0.6

The low mean preoperative value in non-survivors was due to the values observed in two cases of hilar cholangiocarcinoma (both with recent acute phase response from transient cholangitis, after endoscopic biliary drainage), and in two cases of hepatocarcinoma (a 79 year old patient with liver fibrosis and a younger cirrhotic patient with the highest Child-A score, borderline with Child-B)

[a] Last measurement before discharge or death

Table 2. Regressions with the main correlates of plasma albumin (ALB, g/dl)

1. $CHE = 287.4(2.014)^{ALB}$	$r = 0.73$
2. $CHOL = 16.5(1.610)^{ALB}\ (1.001)^{ALKPH}$	$r = 0.71$
3. $CA = 6.2 + 0.7(ALB)$	$r = 0.66$
4. $IBC = 68.6(1.391)^{ALB}$	$r = 0.64$
5. $PROT = 2.8 + 0.9(ALB)$	$r = 0.62$
6. $PA = 13.8 + 16.0(ALB)$	$r = 0.51$
7. $BUN = 21.3 + 20.2(CREAT) - 6.2(ALB)$	$r = 0.91$
8. $ALB = 5.0 - 0.013(AGE) - \{0.5 + 0.003(AGE)_{COMPL} + 0.012(AGE)_{DEATH}\}_{POSTOP}$	$r = 0.74$

Symbols and units: pseudo-cholinesterase (CHE, U/l, nv 5300-13000), cholesterol (CHOL, mg/dl), alkaline phosphatase (ALKPH, U/l, nv 98-279), calcium (CA, mg/dl), iron binding capacity (IBC, mg/dl), total protein (PROT, g/dl), prothrombin activity (PA,% of standard reference), blood urea nitrogen (BUN, mg/dl), creatinine (CREAT, mg/dl), age (AGE, years); r = coefficient of correlation, reflecting the strength of each correlation (range 0.0–1.0). The regressions provide mean quantitative estimates of the relationships between ALB and the simultaneously observed values of the other variables. The non-linear regressions 1, 2 and 4 account for the progressively larger increases in these variables observed with increasing ALB (and for the opposite effect with decreasing ALB), a pattern best reproduced by functions using ALB as an exponent. For instance regression 1 allows the estimation of a mean CHE of 1166 for ALB = 2.0, of 3332 for ALB = 3.5, and of 9523 for ALB = 5.0. Source of non-linear functions: $\log y = a + b(ALB)$, $y = e^{a + b(ALB)} = e^{a}(e^{b})^{ALB}$. The last regression combines AGE with discontinuous variables: measurements performed postoperatively (POSTOP), in patients with complications (COMPL), in non-survivors (DEATH). The coefficients labelled with these subscripts estimate the mean change in slope or intercept associated with the condition in the subscript; if the condition does not occur, the coefficient is zero. Thus the regression accounts simultaneously for a mean decrease in ALB per year increase in age common to all measurements (−0.013 g/dl/year), for a further decrease related to the postoperative condition (−0.5 g/dl), and for additional decreases per year increase in age observed postoperatively in patients with complications (−0.003 g/dl/year) and particularly in non-survivors (−0.012 g/dl/year). These simple variables explained 55% of the variability of ALB ($r = 0.74$, $r^2 = 0.55$). $P < 0.001$ for each regression and each coefficient in the regressions

count ($r = 0.41$ to 0.36, $p < 0.001$ for all), and even more weakly or not significantly to other variables. Multiple regression analysis showed that ALB modulated the direct relationships found between CREAT, BUN and urate (being correlated inversely with BUN and directly with urate for any given CREAT level) (Table 2), between sodium and chloride (being correlated directly with sodium for any given chloride level), and between FIBR and globulins thus reconfirming a previously described interdependency between these variables (Geigy, 1963) ($p < 0.001$ for all correlations). In non-survivors ALB was inversely related to plasma globulin concentration ($r = 0.40$, $p < 0.01$). All the described relationships did not vary significantly between preoperative and postoperative measurements, which all laid in a similar continuous distribution of observations. The best single correlate of ALB was plasma CHE, which explained 53% of its variability ($r = 0.73$, $r^2 = 0.53$) in a non-linear best fit; this fit was improved only by accounting simultaneously for the presence of primary liver malignancy, which was associated with lower CHE for any given ALB ($r = 0.78$, $p < 0.001$), and was not improved by other clinical variables. A similar best fit with CHOL was modulated by the simultaneous level of ALKPH (or of gamma-glutamyltranspeptidase) which accounted for the simultaneous effect of cholestasis on CHOL (Giovannini et al., 2003; Chiarla et al., 2004). Autocorrelations between postoperative and preoperative ALB showed direct correlations of variable strength: the r value was 0.47 at postoperative day 1, increased to 0.68 and 0.77 at day 3 and 7, respectively, and decreased again thereafter to 0.46 in patients with complications ($p < 0.001$ for all). Multiple regression analysis showed that most of the variability of ALB in postoperative measurements was explained by the simultaneous changes in CHE, CHOL, PA, FIBR and the baseline preoperative ALB (multiple $r = 0.87$, $p < 0.001$), while HCT lost significance when considered together with any one of these variables. Amongst non-biochemical variables, ALB was related inversely to patient age ($r = 0.45$, $p < 0.001$), both preoperatively and postoperatively with the same mean estimated coefficient ($dALB/dAGE = -0.013$ g/dl/year). Postoperatively this relationship also became a function of outcome, and the

decrease in ALB per year increase in age became significantly larger in patients with complications (mostly sepsis and/or liver insufficiency) and in particular in those who died, compared to those who recovered normally (Table 2). This relationship was not significantly altered by the simultaneous inclusion of other non-biochemical variables, although in simple regressions ALB was weakly and inversely related to the presence of malignancy and to ASA score, and weakly and directly related to body weight ratio, body mass index and, in postoperative measurements, to doses of exogenous albumin ($r \leq 0.36$, $p < 0.01$ for all). A trend for an inverse relationship with the presence of cirrhosis did not reach significance, probably owing to the selection of patients in good condition (Child-A) as surgical candidates. The inverse correlation between ALB and AGE was only in small part mediated by a trend for lower ALB and higher AGE in patients with primary tumors. In addition to ALB, other variables significantly related to age were CHE, FIBR, phosphate (inverse correlations), and BUN and urate for any given CREAT (direct correlations) ($r \leq 0.37$, $p < 0.001$ for all). Autocorrelations within these variables showed that postoperative CHE, CHOL and FIBR were directly related to preoperative values ($r = 0.61$ to 0.54, $p < 0.001$ for all). With regard to the correlation between ALB and dose of exogenous albumin, this was assessed extensively also in sub-groups of patients at various postoperative times; the only relevant finding was a direct correlation at postoperative day 1 with the doses administered in the previous 24 hours (intra- and postoperatively) ($r = 0.36$, $p < 0.01$). Interestingly, this was associated (only at day 1) with a direct correlation between systolic blood pressure, or pulse pressure, and ALB ($r = 0.46$, $p < 0.001$). Finally, in patients undergoing parenteral nutrition, there was the tendency for a direct relationship between ALB and AA dose ($p \cong 0.05$), which was accounted for mostly by the branched chain AA component.

Regressions based on relative changes in postoperative ALB (the ratio or the difference between postoperative and preoperative ALB) basically reconfirmed the results already found for absolute ALB values, however with weaker coefficients of correlation. Finally, with regard to previously published findings on the prognostic relevance of early postoperative reductions in FIBR, CHOL and phosphate (Giovannini et al., 2004) ALB was also evaluated in conjunction with these variables. In discriminant analysis, the values of ALB and FIBR at postoperative day 1 and 3, together with that of CHOL at day 3 allowed the correct classification of 90% of patients with regard to final outcome ($p < 0.001$); this figure decreased to less than 80% for the simple prediction of complications ($p < 0.001$), and this was related to a stronger predictive power of low ALB with regard to outcome compared to development of complications. The prediction was slightly improved by inclusion of phosphate in the 59 patients in whom it was available. Although remarkable, these findings still need validation and quantification on a larger number of patients before their prognostic use can be assessed.

Discussion

After liver resection, changes in ALB reflect the balance between several factors, which may include altered albumin synthesis (from acute phase response and/or liver dysfunction), loss of albumin from bleeding or catabolism, its redistribution in extravascular space, hemodilution with crystalloids and exogenous albumin administration. This study provides quantitative references and a detailed map for the correlations between ALB and clinical and biochemical variables, and shows that changes in ALB are linked to multiple pathophysiologic events. The direct correlations found with variables reflecting adequacy of hepatic protein synthesis (CHE, IBC, PA and FIBR), without a relevant impact of HCT and other variables related to bleeding and reinfusions, suggest that hemodilution does not play a relevant role, while altered synthesis (or altered synthesis unable to compensate for albumin loss or redistribution) is a more important determinant of hypoalbuminemia. This is also supported by the direct relationship found with FIBR, which is contrary to the common expectancy (fibrinogen is a positive and albumin a negative acute phase protein) and suggests a common denominator such as altered protein synthesis for the parallel changes in ALB and FIBR. This aspect has already been addressed previously (Giovannini et al., 2004). The autocorrelations between postoperative and baseline ALB indicate that the preoperative determinants of ALB are still maintaining a significant role in determining postoperative levels. Furthermore, the fact that the best correlates of ALB combined in a multiple regression predicted ALB with $r = 0.87$ indicates that severity of hypoalbuminemia also represents a cumulative index of severity of illness accounting simultaneously for altered hepatic function, stress-induced extravascular redistribution and protein catabolism. This is also consistent with the inverse relationship found between ALB and BUN for any given CREAT (Table 2) suggesting a contribution of increased catabolic drive to hypoalbuminemia. The good direct correlations found with PROT and CA were more

obvious findings, because albumin accounts for a large part of total plasma protein, and binds a large part of circulating calcium. Indeed, the regression found with CA (Table 2) is very similar to a commonly used formula for the estimation of the impact of changes in ALB on CA levels (Wooley et al., 2005).

The correlations with non-biochemical variables showed a direct relationship between systolic or pulse blood pressure and ALB at postoperative day 1, which emphasizes the role of albumin in the maintenance of hemodynamic stability in the early postoperative period. At this time ALB was also weakly but significantly related to the exogenous albumin dose administered in the previous 24 hours ($r = 0.36$, $p < 0.01$). At all other times this relationship was much weaker or non-significant. This may partly be explained by the fact that low ALB was a reason to administer albumin, but supports also the concept that the underlying pathophysiologic factors are more powerful determinants of ALB than albumin administration (Vincent et al., 2003). Indeed, in individual cases receiving large albumin doses, there was a steady increase in ALB only in those who were steadily recovering from severe illness (sepsis, transient liver insufficiency), while the increase in ALB was undetectable or very transient in persistently severe or terminal illness. This is confirmed by the weak correlation found with baseline ALB at postoperative day 1 ($r = 0.47$) reflecting the dominant impact of the recent stress of surgery, the stronger correlations found at day 5 and 7 ($r = 0.68$ and 0.77, respectively) reflecting progressive pathophysiologic compensation and tendency to recover the original pattern, and the weak correlation found again thereafter in complicated patients, reflecting the overbearing impact of complications and desperate illness.

Particularly relevant is the relationship found between ALB, age and outcome (Table 2) showing how ALB decreased with age and how, postoperatively, this decrease became larger in patients with complications and even more pronounced in non-survivors. This progression of effects is consistent with the concept that hypoalbuminemia is a marker of pathophysiologic frailty associated with increasing age and amplified by the challenges of severe sepsis, liver insufficiency and life-threatening illness. In addition to ALB, other variables suggesting a modified expression of the acute-phase response associated with ageing were decreasing CHE, FIBR and phosphate, and increasing BUN and urate for any given CREAT. These data fit with the evidence of an age-related decrease in margin of reserve for adaptation to acute stress (Fabbri et al., 1994; Kimura et al., 1996; Suttner et al., 2001) which becomes more evident postoperatively. In the elderly patient the involved components extend beyond the simple stress of surgery (parenchymal transection, ischemia, reduction of liver mass) on the aged liver, but include additional factors such as the challenges of complications, the impaired capability to control infection and self-injury from amplification of the acute phase response, and the impaired capability of other systems; the situation may be different after the transplantation of cadaveric liver grafts from elderly donors into young recipients.

Our findings also underscore the prognostic value of preoperative hypoalbuminemia with regard to surgical risk. Indeed, although the low mean preoperative ALB in our non-survivors appeared partly mediated by a circumstantial event (recent transient cholangitis after endoscopic biliary drainage in two cases), in recent years this event has been recognized as a specific risk factor for liver surgery, and its contribution to decrease in ALB highlights the prognostic importance of preoperative hypoalbuminemia. With regard to the practical implications of severe postoperative hypoalbuminemia, it is yet unclear to what extent it is just a component of the general disruption of pathophysiologic balance, or it actively contributes to the disruption with a loss of protection on physiologic homeostasis. For instance, with regard to impaired antioxidant protection, the issue may not be limited simply to hypoalbuminemia because, as we also found, low ALB tends to be associated with low levels of CHOL (reflecting hypolipoproteinemia and reduced transport of vitamin E in lipoproteins), of IBC (reflecting a decrease in the antioxidant transferrin), of urate (also accounting for a loss of antioxidant capacity of plasma) (Giovannini et al., 2003, in press) and of other antioxidants (Chiarla et al., 2000).

In conclusion our data show that hypoalbuminemia after liver resection is not an isolated event, but has a central role within a large series of biochemical and pathophysiologic correlations where degree of hypoalbuminemia may cumulatively reflect severity of illness, with prognostic implications. The relationship with age suggests that low ALB is also a marker of pathophysiologic frailty, associated with ageing and amplified by the challenges of severe sepsis, liver insufficiency and life-threatening illness.

Acknowledgements

This work was supported by a contribution from the Catholic University and the Italian Ministry for University and Scientific Research (D.1 Funds).

The kind assistance of Ms. Helen Raiswell and Mr. Maurizio Cianfanelli is also acknowledged.

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