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Factors Predicting Nutritional Derangements in Patients with Obstructive Jaundice: Multivariate Analysis

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Abstract. Patients with obstructive jaundice (OJ) that requires surgery often have malnutrition associated with increased perioperative morbidity. This study investigated the factors influencing nutritional derangements in these patients. A series of 46 OJ patients were investigated prospectively (28 malignant tumors, 18 benign obstructions). A nutritional risk index of < 83.5 was used to define protein-calorie malnutrition. Liver function, cholecystokinin (CCK), tumor necrosis factor-α (TNFα), and endotoxin levels were determined. A multivariate analysis was performed, and an obstructive jaundice malnutrition index (OJMI) was obtained. Altogether, 22 (48%) OJ patients had malnutrition (33% with benign obstructions, 57% with malignant disease). Malnourished patients had higher serum bilirubin levels (258 ± 120 vs. 154 ± 62 mmol/L; $p = 0.005$), longer duration of jaundice (16 ± 9 vs. 9 ± 5 days; $p = 0.03$), and higher plasma levels of CCK (4.0 ± 1.3 vs. 1.7 ± 1.0 pmol/L; $p = 0.005$), alanine aminotransferase (ALT) (226 ± 209 vs. 187 ± 161 UI/L; $p = 0.01$), endotoxin (15 ± 10 vs. 6.5 ± 7.0 EU/L; $p = 0.007$), and TNFα (69 ± 82 vs. 23 ± 15 pg/ml; $p = 0.008$) than those without malnutrition. However, only serum bilirubin, CCK, ALT, and patient age were predictors for malnutrition by multivariate analysis. Malnutrition might be expected (95% confidence interval) in patients older than 68 years with increased bilirubin (> 290 mmol/L) and ALT (> 210 UI/L) levels that corresponded with an OJMI > 55. It was concluded that nutritional alterations in patients with obstructive jaundice were determined by the intensity of the biliary obstruction correlated with increased plasma CCK levels as well as with liver dysfunction and patient age.

Perioperative complications in patients with obstructive jaundice may be aggravated by disturbances in nutritional status. Controlled studies suggest that treatment of nutritional deficiencies may improve the outcome of surgery [1–3]. Thus identification of prognostic factors is of value in the surgical treatment of patients with obstructive jaundice [1–3]. Malnutrition has previously been observed in patients with benign and malignant biliary obstructions [4, 5]. The high incidence of malnutrition in obstructive jaundice-related neoplasia may be caused by the tumor per se and by the anorexic properties of tumor necrosis factor-α (TNFα) [6]. Malnutrition in patients with benign biliary obstruction is also reported to be considerable [4]. It is therefore important to identify the factors associated with the pathophysiology of the biliary obstruction that might cause malnutrition.

Although short periods of biliary obstruction rarely induce malnutrition, prolonged obstruction of the bile duct with low bile acid secretion may affect fat absorption [7, 8]. It has also been suggested that the presence of endotoxins, a systemic increase in bile component levels [9], and liver dysfunction [10] may lead to anorexia. Miyasaka et al. [11] reported that patients with obstructive jaundice presented increased cholecystokinin (CCK) concentrations. This hormone has powerful anorectic properties [12–14] and has been shown in experimental studies to reduce food intake [15, 16].

It is not yet known whether circulating concentrations of TNFα, endotoxin, bile acids, or CCK are associated with malnutrition in patients with obstruction of the biliary tract. The purpose of this study was to identify factors related to the preoperative derangements in the nutritional status of patients with biliary tract obstruction.

Materials and Methods

A group of 46 patients with obstructive jaundice (20 men, 26 women) were investigated prospectively. Their mean age was 69 ± 11 years. Altogether 18 patients had benign pathologies (12 choledocolithiasis, 6 Mirizzi syndrome), and the remaining 28 had malignant tumors (9 periampullary tumors, 4 gallbladder tumors, 9 hilar tumors, 6 cholangiocarcinomas). Biochemical and hormonal parameters were analyzed in a control group of 18 healthy subjects similar in age (67.5 ± 12.0 years; range 37–76 years) and gender distribution (9 men, 11 women) to the study group.

Patients with the following criteria were included: serum bilirubin > 5 mg/dl, alkaline phosphatase > 150 IU/L, and ultrasonographic evidence of extrahepatic and intrahepatic bile duct dilation (> 4 mm and 8 mm, respectively). Patients meeting the following criteria were excluded: those with acute cholangitis, body temperature > 38°C, intravenous fluid therapy, use of diuretics, parenchymal liver disease, ascites, heart failure, chronic renal failure.

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Nutritional Assessment

Nutritional assessment included anthropometric parameters [ideal body weight (%); mid-arm muscle area (cm^2); skinfold thickness (mm): biceps, triceps, subscapular, suprailiac crest]; visceral proteins [albumin (g/L), transferrin (g/L), prealbumin (mg/L), retinol-binding protein (mg/L)]; creatinine height index (%); and total lymphocyte count (cells/mm^3). Skinfold thickness was measured using a Holtain caliper (pressure 10 g/mm^2). All anthropometric measurements were performed by the same experienced observer.

Protein-calorie malnutrition was defined when the Nutritional Risk Index (NRI) was < 83.5. The NRI was calculated from the following equation [17].

$$NRI = 1.519 \times albumin\ (g/L) + 0.417\ (weight\ [kg]\ on\ admission/usual\ weight\ [kg]) \times 100$$

Biochemical Parameters

Bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transpeptidase (γ-GT) were measured by direct spectrophotometry using a Synchron CX7 analyzer (Beckman-Astra, Brea, CA, USA) [18].

The CCK determination was performed by a sensitive radioimmunoassay (RIA) with plasma extraction through affinity columns (Waters Sep-Pak C-18, Barcelona, Spain), and reconstituted with assay buffer [19, 20]. OAL-656 antiserum was used for the CCK determination. This antiserum recognizes the sulfated tyrosine residue of CCK-8 and CCK-33 (which constitutes more than 80% of CCK recovered from human plasma) but did not cross react with the non sulfated form of CCK-8 (0.04%), gastrin-17 (0.2%), or sulfated gastrin-17 (0.9%). The ^{125}I-labeled Bolton-Hunter CCK-8 reagent was used to label CCK-8 to provide a tracer for the CCK assay. Measurements were made in duplicate on a gamma scintillator (Ultraogamma Counter-INa, Crystal 2-5400 B-5412; Packard, Camberra, Australia). The sensitivity of the assay was 1.2 pmol/L plasma. The intraassay and interassay variation coefficients for these measurements were 5.6% and 6.2% respectively.

Endotoxin was measured using the E-TOXATE kit (Sigma, St. Louis, MO, USA), for the *Limulus* semiquantitative test [21, 22]. TNFα in serum was quantified by competitive enzyme immunoassay [enzyme-linked immunosorbent assay (ELISA)], as previously described [23].

Statistical Analysis

The sample size was estimated. A previous study recorded a mean ± SD difference in albumin values of 5 ± 4 g/L between patients with benign and malignant obstruction [4]. Assuming a 95% confidence interval (CI) and a power of 90%, 14 patients would be required in each group to detect differences of 5 g/L.

Results are expressed as the means ± SD ($p \geq 0.05$). Intergroup and intragroup statistical analyses were performed using the two-tailed Student *t*-test for unpaired and paired data. Correlation of variables was evaluated using Pearson's coefficient. Multivariate analysis was performed to identify prognostic factors for malnutrition. Potentially useful covariables included age, gender, etiology, biochemical parameters of cholestasis, duration of jaundice, parameters indicative of liver function, CCK, TNFα, and endotoxin. Variables for which $p > 0.1$ were excluded from the regression study using the "stepwise method" and were adjusted to the methodologic selection procedure. An obstructive jaundice malnutrition index (OJMI) was obtained with this method.

Table 1. Nutritional parameters for benign and malignant obstructions.

Parameters	Benign obstruction ($n = 18$)	Malignant tumor ($n = 28$)
Ideal body weight (%)	97.0 ± 10.7	88 ± 15*
Skinfold thickness (mm)		
Triceps	15.0 ± 6.5	13 ± 8
Biceps	14 ± 7	13.0 ± 6.5
Subscapular	15 ± 8	12.0 ± 9.5
Iliac	16.5 ± 12.0	15 ± 6
Mid-arm muscle area (cm^2)	27 ± 11	23 ± 9
Visceral proteins		
Albumin (g/L)	35 ± 3	30 ± 4**
Transferrin (g/L)	2.0 ± 0.6	1.7 ± 0.4
Prealbumin (mg/L)	139 ± 48	124 ± 52
RBP (mg/L)	41 ± 18	38 ± 17
TLC (cells/mm^3)	1583 ± 690	1130 ± 473***

Values are means ± SD.
RBP: retinol-binding protein; TLC: total lymphocyte count.
*$p = 0.03$; **$p = 0.001$; ***$p = 0.02$.

Results

The mean serum bilirubin level in patients with obstructive jaundice was 230 ± 110 mmol/L, and the mean duration of jaundice was 13.0 ± 8.7 days. On admission, 22 patients (48%) were malnourished (33% with benign obstruction, 57% with malignant tumors). The mean weight loss in the 46 patients studied was 7.5% ± 4.6% of body weight.

Table 1 provides a comparison between benign and malignant obstructions. Only weight loss, serum albumin, and total lymphocyte count were significantly worse in patients with malignant tumors. A negative correlation was recorded between the serum albumin level and both bilirubin ($r = -0.62$; $p = 0.002$) and CCK ($r = -0.42$; $p = 0.001$) levels.

Table 2 shows the results of biochemical analyses in patients with biliary tract obstruction and healthy controls. Liver enzymes, prothrombin activity, CCK, TNFα, and endotoxin levels were significantly higher in patients with obstructive jaundice. A correlation between the CCK plasma concentration and bilirubin was observed with both benign obstruction ($r = 0.46$; $p = 0.03$) (Fig. 1) and malignant tumors ($r = 0.54$; $p = 0.005$) (Fig. 2).

Cholestasis parameters, duration of jaundice, ALT, plasma concentrations of CCK, TNFα, and endotoxins were significantly higher in malnourished than in nonmalnourished patients (Table 3). The behavior of these variables was identical when the results for either benign or malignant obstructive jaundice were analyzed according to the nutritional status, except TNFα. Plasma levels of TNFα increased only in malnourished patients with neoplasia (78.0 ± 77.0 pg/ml in malnourished patients versus 20.0 ± 8.6 pg/ml in nonmalnourished patients) ($p = 0.002$). In patients with benign obstruction the TNFα plasma concentrations showed little difference (24 ± 30 pg/ml in malnourished patients versus 33 ± 40 pg/ml in nonmalnourished patients).

Table 2. Results of biochemical parameters analyzed in obstructive jaundice patients and controls.

Parameters	OJ (n = 46)	Controls (n = 18)	p
Bilirubin (mmol/L)	230 ± 120	13.5 ± 8.5	0.0002
Alkaline phosphatase (IU/L)	817 ± 868	88 ± 25	0.002
γ-GT (IU/L)	628 ± 678	35 ± 13	0.001
AST (IU/L)	172 ± 175	37 ± 23	0.004
ALT (IU/L)	205 ± 188	36 ± 27	0.001
Prothrombin activity (%)	97 ± 6	NA	NA
CCK (pmol/L)	2.8 ± 1.4	1.2 ± 0.2	0.0006
Endotoxin (EU/ml)	12.0 ± 9.6	<0.75	0.0001
TNFα (pg/ml)	46.5 ± 62.0	28 ± 13	0.06

Values are means ± SD.

NA: not available; OJ: obstructive jaundice group; γ-GT (γ-glutamyl transpeptidase); AST (aspartate aminotransferase); ALT (alanine aminotransferase); CCK (cholecystokinin); TNFα (tumor necrosis factor-α).

When a multiple logistic regression was applied that included all parameters, only the serum bilirubin, ALT, and CCK proved to be reliable predictors of malnutrition in patients with obstructive jaundice (Table 4). For clinical purposes, a multiple logistic regression, excluding the nonroutine available parameters (CCK, TNFα, endotoxin) was performed. Serum bilirubin, ALT, and patient age were the predicting factors for malnutrition (Table 5).

The logistic equation obtained as the OJMI was

$$OJMI = 24 + 0.05\,ALT + 0.03\,bilirubin + 0.1\,age$$

Patients with a nutritional index > 55 were malnourished. The sensitivity and specificity of the equation to detect malnutrition were 82% and 83%, respectively. Positive and negative predictive values of the equation were 89% (95% CI 79–98%) and 75% (95% CI 63–88%), respectively. Malnutrition might be expected (95% CI) in jaundiced patients older than 68 years with serum bilirubin > 290 mmol/L and ALT > 210 UI/L.

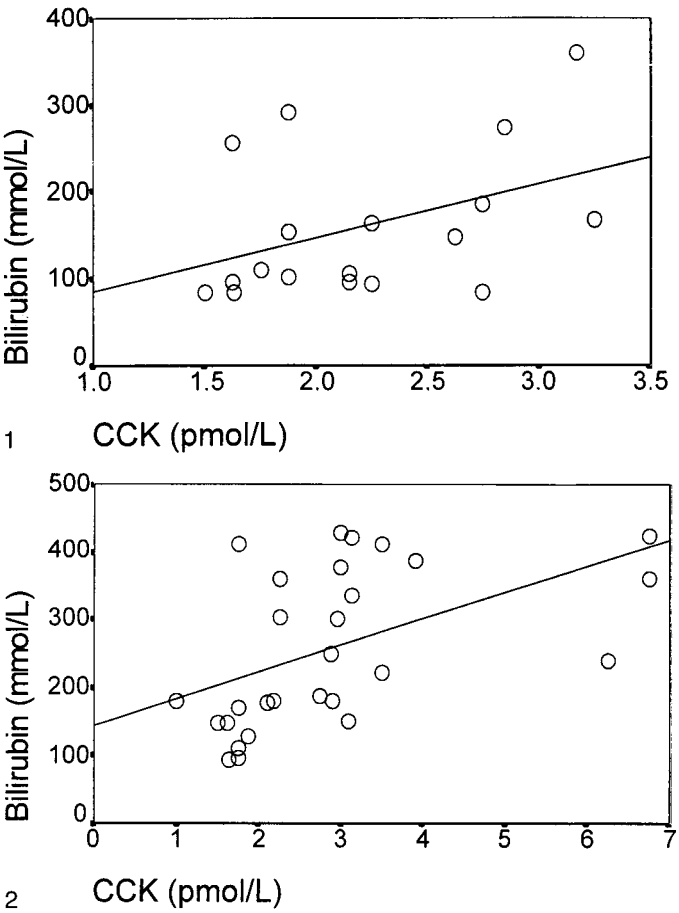

Fig. 1. Correlation between serum bilirubin and cholecystokinin (CCK) in patients with benign obstruction ($r = 0.46$; $p = 0.03$). Equation of linear regression: $y = 1.55 + 0.87x$.

Fig. 2. Correlation between serum bilirubin and CCK in patients with malignant obstruction ($r = 0.54$; $p = 0.005$). Equation of linear regression: $y = 7.6 + 0.6x$.

Discussion

This study analyzed various factors potentially related to the nutritional status of patients with obstruction of the biliary tract. Of the factors studied, those associated with malnutrition were the intensity of the bile duct obstruction associated with increased CCK plasma levels, liver dysfunction, and the patient's age.

Previous studies have reported a high incidence of malnutrition in patients with obstructive jaundice [4, 5]. However, the degree of malnutrition may be underestimated in these patients owing to abnormally increased serum albumin concentrations resulting from depleted extracellular and plasma volume [24, 25] associated with alterations in sodium- and water-regulating hormones [26, 27].

As observed in a previous study [4], weight loss and low serum albumin concentrations were considerably more marked in patients with a malignant obstruction. Low serum albumin levels in cancer patients may be accounted for by a chronic reduction in food intake and protein-calorie malnutrition, or they may result from an acute-phase response secondary to the activity of TNFα and other proinflammatory cytokines that down-regulate albumin synthesis and induce an increase in energy expenditure [28–30]. TNFα is a cytokine that acts as a cachectin associated with cancer and endotoxemic status [31–33]. In the present study, TNFα levels were significantly higher only in the presence of malignant biliary obstruction with malnutrition. In patients with benign obstructive jaundice and who met the malnutrition criteria, plasma TNFα levels were close to those obtained in healthy controls. Although a high incidence of malnutrition was observed in patients with malignant obstructive jaundice, multivariate analysis showed that neither the etiology of the biliary obstruction nor plasma concentrations of TNFα and endotoxin were considered prognostic factors for malnutrition.

Contrary to expectations, the duration of jaundice was not predictive of malnutrition. However, malnutrition was associated with the intensity of the biliary obstruction, according to the plasma bilirubin levels. These findings suggest that an absence of bile in the duodenum may induce stimulation of anorexia mediators. In the present study, an increase in CCK was observed in patients with obstructive jaundice and malnutrition compared to that in patients with normal nutritional status, whose CCK levels were close to those of healthy controls. Moreover, the correlation

Table 3. Evaluation of analyzed parameters according to nutritional status.

Parameter	Malnourished ($n = 22$)	Not malnourished ($n = 24$)	p
Duration of jaundice (days)	16 ± 9	9 ± 5	
Bilirubin (mmol/L)	258 ± 120	156 ± 62	0.005
Alkaline phosphatase (IU/L)	1017 ± 1168	383 ± 358	0.008
γ-GT (IU/L)	616 ± 666	301 ± 297	0.03
AST (IU/L)	184 ± 206	152 ± 105	NS
ALT (IU/L)	226 ± 209	187 ± 161	0.01
Prothrombin activity (%)	95.0 ± 6.5	99.5 ± 5.0	0.052
CCK (pmol/L)	4 ± 1.3	1.7 ± 1.0	0.005
Endotoxin (EU/L)	15 ± 10	6.5 ± 7.0	0.007
TNFα (pg/ml)	69 ± 82	23 ± 15	0.008

Values are means ± SD.

Table 4. Results of multiple logistic regression applied for malnutrition in obstructive jaundice patients, including all parameters analyzed.

Variable	Coefficient	SE	Wald	p	OR
Bilirubin	0.04	0.13	6	0.01	1.35
CCK	0.2	0.13	5.5	0.03	1.2
ALT	0.09	0.01	2	0.05	0.9
Constant	21	2	8	0.005	

SE: standard error; Wald: statistic that tests the null hypothesis that a coefficient in a logistic regression model is zero; OR: odds ratio.

between CCK and malnutrition proved statistically significant by multivariate analysis.

Clinical studies suggest that the presence of bile in the gut exerts negative feedback on CCK secretion [34, 35]. By contrast, in patients with biliary tract obstruction, the absence of bile in the duodenum and the consequent accumulation of bile components in the blood was accompanied by increased plasma CCK levels. CCK is involved in biliopancreatic physiology, stimulating the secretion of bile and pancreatic enzymes. Several studies have shown that CCK has considerable anorectic properties [12–14, 36, 37]. CCK acts as a neuropeptide in the central nucleus of satiety and in the digestive tract by slowing down the rate of gastric emptying.

Finally, malnutrition is known to be more frequent in patients with marked liver dysfunction and low anabolic capacity [10]. Nevertheless, obstruction of the biliary tract usually leads to moderate impairment of liver function, as observed here. In the present study, patients who met malnutrition criteria had higher ALT levels than those without malnutrition. Moreover, ALT plasma concentrations remained in the logistic regression equation as a prognostic factor for malnutrition.

Based on our data, for perioperative management special attention should be paid to patients with obstructive jaundice who are older than 68 years and have high plasma bilirubin and ALT levels, as malnutrition may be expected in these individuals. Preoperative drainage might alleviate some of the nutritional alterations in these patients [21]. Despite proper drainage, though, a postdrainage period longer than 10 days is necessary to improve the overall nutritional status, particularly in those with malignant disease [21]. Perioperative nutritional support might be considered in this selected group of patients with persistent severe malnutrition to reduce the major postoperative complications [1–3, 38].

Table 5. Results of multiple logistic regression applied for malnutrition in obstructive jaundice patients excluding nonroutine parameters (CCK, TNFα, endotoxin).

Variable	Coefficient	SE	Wald	p	OR
Bilirubin	0.03	0.19	7	0.01	1.5
Age	0.1	0.1	4	0.02	1.3
ALT	0.05	0.01	2.5	0.05	1.1
Constant	24	2.5	9.5	0.005	

Conclusions

Malnutrition observed in patients with obstructive jaundice was mainly related to the intensity of the bile duct obstruction, associated with increased plasma CCK levels and the degree of liver dysfunction and the age of the patient. Patients older than 68 years with high plasma levels of bilirubin and ALT (OJMI > 55) displayed an increased risk of severe malnutrition.

Résumé

Fond du problème: Les patients souffrant d'un ictère par obstruction (IO) qui nécessite un geste chirurgical sont souvent dénutris, augmentant ainsi la morbidité périopératoire. Cette étude a examiné les facteurs influençant les perturbations nutritionnelles chez ces patients. Méthodes: Quarante-six patients ayant un IO [28 tumeurs malignes et 18 cas d'obstructions d'origine bénignes] ont été examinés prospectivement. On a défini la malnutrition en calories sous forme de protéines par un indexe de risque nutritionnel inférieur à 83,5. On a mesuré la fonction hépatique et les taux de cholécystokinine (CCK), de TNF-α et des endotoxines. Par analyse multifactorielle, on a déterminé un indexe de malnutrition d'ictère par obstruction (IMIO). Résultats: Vingt-deux patients (48%) ayant un IO avaient une malnutrition (33% en cas d'obstruction bénigne, et 57% en cas de maladie maligne). Par rapport aux patients sans malnutrition, les patients dénutris avaient un taux de bilirubine sérique plus élevé (256 ± 120 mmol/L vs 154 ± 62 mmol/L; p = 0,005), une durée plus longue d'ictère (16 ± 9 jours vs 9 ± 5 jours; p = 0,03) et un taux plasmatique augmenté de CCK (4 ± 1,3 pmol/L vs 1,7 ± 1 pmol/L; p = 0,005), des ALAT (226 ± 209 UI/L vs 187 ± 161 UI/L; p = 0,01), d'endotoxines (15 ± 10 EU/L vs 6,5 ± 7 EU/L; p = 0,007) et de TNF-α (69 ± 82 pg/mL vs 23 ± 15 pg/mL; p = 0,008). Cependant, seuls, la bilirubine sérique, le CCK, les ALAT et l'âge des patients étaient prédictifs de malnutrition par analyse multifactorielle. On pourrait s'attendre (IC à 95%) à une malnutrition chez les patients plus âgés que 68 ans avec une augmentation de la bilirubine (> 290 mmol/L) et des ALAT (> 210 UI/L), correspondant à un IMIO plus élevé de 55. Conclusions: Les modifications nutritionnelles chez les patients ayant un IO sont déterminées par l'intensité de l'obstruction biliaire et sont corrélées avec des taux augmentés de CCK plasmatique aussi bien qu'avec la dysfonction hépatique et l'âge.

Resumen

Antecedentes: Los pacientes con ictericia obstructiva (IO) que requieren cirugía con frecuencia exhiben malnutrición, la cual se asocia con aumento de la morbilidad perioperatoria. El presente estudio buscó determinar los factores que influyen sobre las

alteraciones nutricionales en estos pacientes. Métodos: Cuarenta y seis pacientes con IO (28 tumores malignos y 18 obstrucciones benignas) fueron investigados en forma prospectiva. Se utilizó un índice de riesgo nutricional menor de 83.5 para establecer el diagnóstico de desnutrición calórico-proteica. Se hicieron determinaciones de función hepática, colecistoquinina (CCK), TNF-∝ y niveles de endotoxina. Se derivó un índice de malnutrición de ictericia obstructiva (IMIO) mediante análisis multivariable. Resultados: Veintidós (48%) de los casos tenían malnutrición (33% en la obstrucción benigna y 57% en la enfermedad maligna). Los pacientes con desnutrición presentaron niveles más altos de bilirrubina sérica (256 ± 120 mmol/L vs 154 ± 62 mmol/L; p = 0.005), más larga duración de la ictericia (16 ± 9 días vs. 9 ± 5 días; p = 0.03) y más altos niveles plasmáticos de CCK (4 ± 1.3 pmol/L VS 1.7 pmol/L; p = 0.005), de ALT (226 ± 209 UI/L vs 187 ± 161 UI/L; p = 0.01) endotoxina (15 ± 10 EU/L vs 6.5 ± 7 EU/L; p = 0.007) y TNF-∝ (69 ± 82 pg/ml vs 23 ± 15 pg/mL; p = 0.008) que aquellos que no tenían malnutrición. Sin embargo, sólo la bilirrubina sérica, la CCK, la ALT y la edad del paciente fueron factores de predicción de malnutrición en el análisis multivariable. Se debe sospechar malnutrición (CI95%) en pacientes mayores de 68 años con incremento de la bilirrubina (> 290 mmol/L) y de la ALT (> 210 UI/I) que corresponde a un IMIO mayor de 55. Conclusiones: Las alteraciones nutricionales en pacientes con ictericia obstructiva fueron determinadas mediante la intensidad de la obstrucción biliar correlacionada con incrementos en los niveles plasmáticos de CCK, con disfunción hepática y con la edad.

References

1. Mullen, J.L., Buzby, G.P., Mattews, D.C.: Reduction of operative morbidity and mortality by combined preoperative and postoperative nutritional support. Ann. Surg. *192*:604, 1981
2. Buzby, G.P., Williford, W.O., Peterson, O.: A randomized clinical trial of TPN in malnourished surgical patients: the rationale and impact of previous clinical trials and pilot study on the protocol design. Am. J. Clin. Nutr. *47*:357, 1988
3. Muller, J.M., Brenner, U., Dients, C.: Preoperative parenteral feeding in patients with gastrointestinal carcinoma. Lancet *1*:68, 1982
4. Padillo, F.J., Gallardo, J.M., Naranjo, A., Rodriguez, M., Miño, G., Sitges-Serra, A., Pera-Madrazo, C.: Changes in the pattern of visceral proteins after internal biliary drainage in patients with obstructive jaundice. Eur. J. Surg. *165*:550, 1999
5. Ishida, Y., Nagao, T., Uchida, H.: Nutritional and immunological assessment in patients with malignant obstructive jaundice: the influence of preoperative biliary decompression and abdominal surgery. Nippon Geka Gakkai Zasshi *95*:71, 1994
6. Smith, B.K., Kenger, M.J.: Anti-TNF-alpha antibodies normalized body temperature and enhanced food intake in tumor-bearing rats. Am. J. Physiol. *265*:15, 1993
7. Rege, R.V.: Adverse effects of biliary obstruction: implications for treatment of patients with obstructive jaundice. A.J.R. *164*:287, 1995
8. Sherlock, S.: Diseases of the Liver and Biliary System. Boston, Blackwell Scientific, 1989, pp. 248–272
9. Trarlos, G.S., Mooris, R.W., Elwell, M.R., Dukc, A., Rosemblum, S., Thompson, M.B.: Frequency and relationships of clinical chemistry and liver and kidney histopathology findings in 13-week toxicity studies in rats. Toxicology *107*:17, 1996
10. Herrera, J.L.: Abnormal liver enzyme levels: the spectrum of causes. Postgrad. Med. *93*:113, 1993
11. Miyasaka, K., Funakoshi, A., Matsumoto, M., Nakamura, R., Sakamoto, S., Sakai, H., Kitani, K.: Bile acids in human plasma interfere with cholecystokinin bioassay using dispersed pancreatic acini. Dig. Dis. Sci. *36*:310, 1991
12. Stallone, D., Nicolaidis, S., Gibbs, J.: Cholecystokinin-induced anorexia depends on serotoninergic function. Am. J. Physiol. *256*:1138, 1989
13. Poeschla, B., Gibbs, J., Simansky, K.J., Greenberg, D., Smith, G.P.: Cholecystokinin-induced satiety depends on activation of 5-HT1C receptors. Am. J. Physiol. *264*:62, 1993
14. Butera, P.C., Bradway, D.M., Cataldo, N.J.: Modulation of the satiety effect of cholecystokinin by estradiol. Physiol. Behav. *53*:1235, 1993
15. Tangoku, A., Doi, R., Chowdhury, P., Pasley, J.N., McKay, D.W., Rayford, P.L.: Use of a specific cholecystokinin receptor antagonist (L-364,718) to determine the role of cholecystokinin on feeding and body weight in rats with obstructive jaundice. J. Assoc. Acad. Minor. Phys. *2*:38, 1992
16. Tangoku, A., Chowdhury, P., Huang, Y.S., Doi, R., Blevins, G.T., Jr., Eyiuche, C., McKay, D.W., Rayford, P.L.: Exocrine pancreatic function in obstructive jaundice rats: studies with isolated dispersed pancreatic acini. J. Surg. Res. *53*:378, 1992
17. Veterans Affairs Total Parenteral Nutrition Cooperative Study Group: Perioperative total parenteral nutrition in surgical patients. N. Engl. J. Med. *325*:525, 1991
18. Mashige, F., Tanaka, N., Maki, A., Kamei, S., Yamanaka, M.: Direct spectrophotometry of total bile acids in serum. Clin. Chem. *27*:1352, 1981
19. Gutzwiller, J.P., Drewe, J., Hildebrand, P., Rossi, L., Lauper, J.Z., Beglinger, C.: Effect of intravenous human gastrin-releasing peptide on food intake in humans. Gastroenterology *106*:1168, 1994
20. Garcés, M.C., Gómez-Cerezo, J., Codoceo, R., Grande, C., Barbado, J., Vázquez, J.J.: Postprandial cholecystokinin response in patients with chronic pancreatitis in treatment with oral substitutive pancreatic enzymes. Dig. Dis. Sci. *43*:562, 1998
21. Tomasulo, P.A., Levin, J., Murphy, P.A., Winkelstein, J.A.: Biological activities of tritiated endotoxins: correlation of the Limulus lysate assay with rabbit pyrogen and complement-activation assays for endotoxin. J. Lab. Clin. Med. *89*:308, 1977
22. Wachtel, R.F., Tsuji, K.: Comparison of Limulus amebocyte lysates and correlation with the United States Pharmacopeial pyrogen test. Appl. Environ. Microbiol. *33*:1265, 1977
23. Muntané, J., Montero, J.L., Marchal, T., Pérez-Seoane, C., Lozano, J.M., Fraga, E., Pintado, C., De la Mata, M., Miño, G.: Effect of PgE_1 on TNFα status and hepatic D-galactosamine-induced apoptosis in rats. J. Gastroenterol. Hepatol. *13*:197, 1998
24. Sitges-Serra, A., Carulla, X., Piera, C., Martínez-Rodenas, F., Franch, G., Piera, J., Gubern, J.M.: Body water compartments in patients with obstructive jaundice. Br. J. Surg. *79*:553, 1992
25. Padillo, F.J., Rodriguez, M., Gallardo, J.M., Andicoberry, B., Naranjo, A., Martín-Malo, A., Miño, G., Sitges-Serra, A., Pera-Madrazo, C.: Preoperative assessment of body fluid disturbances in patients with obstructive jaundice. World J. Surg. *23*:681, 1999
26. Valverde, J., Martinez-Ródenas, F., Pereira, J.A., Carulla, X., Jimenez, W., Gubern, J.M., Sitges-Serra, A.: Rapid increase in plasma levels of atrial natriuretic peptide after common bile duct ligation in the rabbit. Ann. Surg. *216*:554, 1992
27. Gallardo, J.M., Padillo, F.J., Martín-Malo, A., Miño, G., Pera-Madrazo, C., Sitges-Serra, A.: Increased plasma levels of atrial natriuretic peptide and endocrine markers of volume depletion in patients with obstructive jaundice. Br. J. Surg. *85*:28, 1998
28. Kowalski-Saunders, P.W.J., Winwood, P.J., Arthur, M.J.P., Wright, R.: Reversible inhibition of albumin production by rat hepatocytes maintained in a laminin-rich gel (Engdbroh-Holm-Susarm) in response to secretory products of Kupffer cells and cytokines. Hepatology *16*:733, 1992
29. Falconer, J.S., Fearon, K.C.H., Plester, C.E., Ross, J.A., Carter, D.C.: Cytokines, the acute-phase response and resting energy expenditure in cachectic patients with pancreatic cancer. Ann. Surg. *219*:325, 1994
30. Fearon, K.C.H., Falconer, J.S., Slater, C., McMillan, D.C., Ross, J.A., Preston, T.: Albumin synthesis rates are not decreased in hypoalbuminemic cachectic cancer patients with an ongoing acute-phase protein response. Ann. Surg. *227*:249, 1998
31. Santi, G., Ilyin, S.E., Plata-Salaman, C.R.: Anorexia induced by cytokine interaction at pathophysiological concentrations. Am. J. Physiol. *270*:1394, 1996
32. Plata-Salaman, C.R.: Anorexia induced by activators of the signal transducer gp130. Neuroreport *7*:841, 1996
33. Sanaf, P., Frederich, R.C., Turner, E.M., Ma, G., Jaskowiak, N.T.,

Rivet, D.J., Flier, J.S., Lowell, B.B., Fraker, D.L., Alexander, H.R.: Multiple cytokines and acute inflammation raise mouse leptin levels: potential role in inflammatory anorexia. J. Exp. Med. *185*:171, 1997
34. Koop, I., Schindler, M., Bosshanmer, A., Scheibner, J., Stange, E., Koop, H.: Physiological control of cholecystokinin release and pancreatic enzyme secretion by intraduodenal bile acids. Gut *39*:661, 1996
35. Koop, I.: Role of bile acids in the control of pancreatic secretion and CCK release. Eur. J. Clin. Invest. *20*:51, 1990
36. Reidelberger, R.D., Varga, G., Liehr, R.M., Castellanos, D.A., Rosenquist, G.L., Wong, H.C., Walsh, J.H.: Cholecystokinin suppresses food intake by a nonendocrine mechanism in rats. Am. J. Physiol. *267*:901, 1994
37. Zittel, T.T., von Elm, B., Teichmann, R.K., Rabould, H.E., Becker, H.D.: Cholecystokinin is partly responsible for reduced food intake and body weight loss after total gastrectomy in rats. Am. J. Surg. *169*:265, 1995
38. Von Meyenfeldt, M.F., Meijerink, W.J.H.J., Rouflart, M.M.J., Builmaassen, M.T.H.J., Soeters, P.B.: Perioperative nutritional support: a randomised clinical trial. Clin. Nutr. *11*:180, 1992