Parenteral Nutrition–Associated Hyperglycemia in Non–Critically Ill Inpatients Increases the Risk of In-Hospital Mortality (Multicenter Study)

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OBJECTIVE—Hyperglycemia may increase mortality in patients who receive total parenteral nutrition (TPN). However, this has not been well studied in noncritically ill patients (i.e., patients in the nonintensive care unit setting). The aim of this study was to determine whether mean blood glucose level during TPN infusion is associated with increased mortality in noncritically ill hospitalized patients.

RESEARCH DESIGN AND METHODS—This prospective multicenter study involved 19 Spanish hospitals. Noncritically ill patients who were prescribed TPN were included prospectively, and data were collected on demographic, clinical, and laboratory variables as well as on in-hospital mortality.

RESULTS—The study included 605 patients (mean age 63.2 ± 15.7 years). The daily mean TPN values were 1.630 ± 323 kcal, 3.2 ± 0.7 g carbohydrates/kg, 1.26 ± 0.3 g amino acids/kg, and 0.9 ± 0.2 g lipids/kg. Multiple logistic regression analysis showed that the patients who had mean blood glucose levels >180 mg/dL during the TPN infusion had a risk of mortality that was 5.6 times greater than those with mean blood glucose levels <140 mg/dL (95% CI 1.47–21.4 mg/dL) after adjusting for age, sex, nutritional state, presence of diabetes or hyperglycemia before starting TPN, diagnosis, prior comorbidity, carbohydrates infused, use of steroid therapy, SD of blood glucose level, insulin units supplied, infectious complications, albumin, C-reactive protein, and HbA_{1c} levels.

CONCLUSIONS—Hyperglycemia (mean blood glucose level >180 mg/dL) in noncritically ill patients who receive TPN is associated with a higher risk of in-hospital mortality.

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Malnutrition is associated with an increased risk of hospital complications, a higher mortality rate, a longer hospital stay, and higher hospitalization costs (1). The beneficial effect of total parenteral nutrition (TPN) in improving the nutritional status of hospitalized patients who are malnourished is well established (2). However, several retrospective and prospective studies have shown that the use of TPN is an independent risk factor for the onset or aggravation of hyperglycemia independently of a history of diabetes (2,3).

Hyperglycemia in hospitalized patients is associated with a higher risk of complications and death, especially when no insulin therapy is used (3–11). So far, though, the published studies almost always involved small groups of intensive care patients (or both critically and noncritically ill patients) from just one center, and all were retrospective. In addition, these studies used classifications of previous diabetes based solely on the clinical history and failed to control the analyses for confounding variables, which may greatly influence both hyperglycemia and mortality (e.g., degree of malnourishment, severity of disease, dose of carbohydrates infused, glycemic variability). Furthermore, because the studies were retrospective, they did not ensure the homogenous collection of capillary blood glucose values, and any lack of data could have influenced results in addition to possibly affecting treatment and prevention algorithms (9).

Clinical practice guidelines and consensus statements recommend a premeal blood glucose level of <140 mg/dL for most noncritically ill patients in conjunction

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with random blood glucose values of <180 mg/dL (12,13). These cut points, however, are derived from studies undertaken in critically ill patients (who often receive TPN and enteral nutritional support), and it is not known whether the results are also applicable to noncritically ill patients receiving TPN because these patients have an increased risk of complications and mortality.

We hypothesized that hospitalized noncritically ill patients receiving TPN with appropriate blood glucose control experience less in-hospital mortality than patients with uncontrolled hyperglycemia. The aim, therefore, of this multicenter study was to determine whether blood glucose levels measured during TPN infusion in noncritically ill patients influence hospital mortality under conditions of daily clinical practice while controlling for confounding variables.

RESEARCH DESIGN AND METHODS

—This multicenter study involved 19 hospitals in Spain (16 university hospitals and 3 nonuniversity hospitals). The study included all hospitalized noncritically ill patients (i.e., patients in the nonintensive care unit [ICU] setting) who started TPN as a sole source of nutrition between September and December 2010. Patients were excluded if they were in ICUs, receiving parenteral nutrition together with enteral nutrition, pregnant, or <14 years of age. The study was approved by the Research Ethics Committee of Carlos Haya Regional University Hospital, and all the participants gave written informed consent.

TPN protocol

The TPN formula at all the hospitals was provided as a total nutrient admixture (3 in 1) solution containing carbohydrates, proteins, and lipids. All patients receiving TPN were seen daily by a member of the hospital nutrition unit, who made adjustments in accordance with the relevant guidelines (14,15). Prospective measurements were made of capillary blood glucose levels every 6 h, but if the blood glucose levels were <140 mg/dL, the measurements were made every 8 h. The blood glucose monitor used was the usual model in each hospital. If a patient had hyperglycemia, insulin treatment was started, following consensus recommendations (12).

Table 1—*Patient and TPN characteristics*

Variable	Value
Age (years)	63.2 ± 15.7
Men/women (%)	56.7/43.3
Days hospitalized (*n*)	33.6 ± 26.7
Days on TPN (*n*)	13 ± 11
BMI (kg/m^2)	25.2 ± 5.5
TPN characteristics	
Kilocalories administered	1.630 ± 323
Kilocalories/kg body weight	25.1 ± 5.7
Carbohydrates (g/kg)	3.2 ± 0.7
Amino acids (g/kg)	1.26 ± 0.3
Lipids (g/kg)	0.9 ± 0.2
Total carbohydrates (TPN + dextrose-containing solutions) (g/kg)	3.8 ± 0.8
Type of amino acids	
Standard formulations	459 (75.9)
Glutamine- and branched amino acid–enriched formulations	146 (24.1)
Type of lipids	
LCT soy based	90 (14.9)
LCT olive based	124 (20.5)
LCT/MCT	249 (41.2)
Omega-3 enriched	139 (23.0)
Capillary blood glucose mean (mg/dL)	140 ± 36.5
HbA_{1c} (%)	5.75 ± 0.8
Blood glucose SD	27.2 ± 18.5
Blood glucose coefficient of variation (%)	18.4 ± 8.8
CRP level (mg/L)	94.3 ± 96.3
Albumin level (g/dL)	2.65 ± 0.62
Malnutrition according to SGA	
Normally nourished	214 (35.4)
Moderate malnutrition	245 (40.5)
Severe malnutrition	146 (24.1)
Diagnosis	
Surgery	360 (59.5)
Oncology (solid and hematologic)	114 (18.8)
Digestive	89 (14.7)
Infectious disorders	42 (6.9)
Diabetes status before TPN infusion	
Normal	308 (50.9)
Hyperglycemia without diabetes	166 (27.4)
Known and unknown diabetes	131 (21.7)

Data are means ± SD or *n* (%) unless otherwise indicated. LCT, long-chain triglycerides; MCT, medium-chain triglycerides.

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Data were recorded on demographic variables; diagnosis on admission; prior comorbidity (history of kidney or liver failure, respiratory or cardiac disease, transplantation); anthropometric data (weight, height, BMI); type of TPN; concomitant prescription of steroids, somatostatin, tacrolimus, or cyclosporin; and nutritional assessment by subjective global assessment (SGA) before starting TPN (16). The mean daily insulin dose was also recorded.

Before starting the TPN infusion, a blood sample was drawn to measure the glycated hemoglobin, following the international recommendations for standardization of the HbA_{1c} measurement (17). Measurements were also made of fasting plasma blood glucose, albumin, and C-reactive protein (CRP) levels (with an autoanalyzer) at the laboratories of each hospital.

Patients were considered to have known diabetes if they had a documented history of diabetes. Patients were considered to have unknown diabetes if there was no record of having had diabetes but the HbA_{1c} was ≥6.5% (18). Any other patient with fasting plasma glucose levels ≥126 mg/dL was considered to have hyperglycemia without diabetes. Hypoglycemia was considered to be a capillary blood glucose level <70 mg/dL. The blood glucose variance was estimated from the SD of the mean blood glucose levels and their coefficient of variation.

The primary end point was all-cause in-hospital death. Other clinical outcome parameters were the number of days in the hospital and infectious complications, as recorded on the patient charts.

Statistical study

The comparisons between the qualitative variables were done with the χ^2 test, with Fisher correction when necessary. The distribution of the quantitative variables was examined with the Kolmogorov-Smirnov test. The differences between the quantitative variables were analyzed with the Student *t* test or ANOVA for two or more samples, respectively. Nonparametric tests (Mann-Whitney or Kruskal-Wallis) were used when the study variables did not follow a normal distribution. The significant associations were later included in multivariate logistic regression models, controlling also for other variables such as age, sex, the presence of diabetes or hyperglycemia before the administration of TPN, insulin dose per kilogram body weight, and glycated hemoglobin level. For all the calculations, significance was set at $P < 0.05$ for two tails.

RESULTS—The study included 605 patients, with a mean of 32 patients per hospital (range 19–55). The characteristics of the patients and the TPN infused are shown in Table 1. The mean HbA_{1c} according to diabetes status was 5.3 ± 0.5% normal (*n* = 308); 5.7 ± 0.4% hyperglycemia without diabetes (*n* = 166); 7.2 ± 1.0% unknown diabetes (*n* = 23); and 6.6 ± 1.1% known diabetes (*n* = 108). TPN was started 10 ± 14 days after admission; 433 (71%) patients received insulin at some time during the TPN infusion (55% subcutaneously, 36% in the bag and subcutaneously, and 9% with insulin perfusion independently of TPN).

There were 58 in-hospital deaths (9.6%). Table 2 shows the characteristics of the patients who died and of those who survived. Significant differences were found in age, length of stay, BMI, total

Table 2—*Characteristics of the patients according to the presence of hospital mortality*

	Death		
Variable	No	Yes	*P* value
Patients (*n*)	547 (90.4)	58 (9.6)	
Age (years)	62.7 ± 15.9	67.9 ± 12.0	0.003
Days hospitalized (*n*)	32.7 ± 26.1	42.0 ± 31.1	0.03
Days on TPN (*n*)	12.9 ± 11.1	15.1 ± 11.2	NS
BMI (kg/m^2)	25.4 ± 5.6	23.6 ± 4.7	0.023
Total kilocalories administered through TPN	1,637.5 ± 327.2	1,567.5 ± 278	NS
Kilocalories/kg body weight	24.9 ± 5.1	26.3 ± 5.4	NS
Total carbohydrates (TPN + dextrose-containing solutions) (g/kg)	3.7 ± 0.8	4.4 ± 0.9	0.004
Amino acids (g/kg)	1.26 ± 0.3	1.30 ± 0.3	NS
Lipids (g/kg)	0.94 ± 0.2	0.98 ± 0.3	NS
Capillary blood glucose mean (mg/dL)	138.5 ± 34.8	154.2 ± 48.2	0.02
HbA_{1c} (%)	5.7 ± 0.8	6.1 ± 1.3	NS
Blood glucose SD	26.6 ± 18.2	33.2 ± 21.2	0.01
Blood glucose coefficient of variation (%)	18.2 ± 8.6	20.5 ± 10.0	NS
CRP level (mg/L)	91.3 ± 95	122.5 ± 104.5	0.026
Albumin level (g/dL)	2.7 ± 0.6	2.4 ± 0.6	0.003
Insulin units/kg body weight	0.17 ± 0.4	0.29 ± 0.4	0.013
SGA			
Normally nourished	205 (95.8)	9 (4.2)	
Moderate malnutrition	221 (90.2)	24 (9.8)	
Severe malnutrition	121 (82.9)	25 (17.1)	<0.001
Use of corticosteroids			
No	459 (92)	40 (8)	
Yes	88 (83)	18 (17)	0.01
Diagnosis			
Surgery	336 (93.3)	24 (6.7)	
Oncology (solid and hematologic)	92 (80.7)	22 (19.3)	
Digestive	84 (94.4)	5 (5.6)	
Infectious disorders	35 (83.3)	7 (16.7)	0.001
Diabetes status before TPN infusion			
Normal	282 (91.6)	26 (8.4)	
Hyperglycemia without diabetes	151 (91)	15 (9)	
Known and unknown diabetes	114 (87)	17 (13)	NS
Previous comorbidity			
No	421 (92.3)	35 (7.7)	
Yes	126 (84.6)	23 (15.4)	0.01
Infectious complications			
No	456 (92.9)	35 (7.1)	
Yes	91 (79.8)	23 (20.2)	<0.001

Data are mean ± SD or *n* (%).

grams of carbohydrates infused, mean capillary blood glucose level, SD of the blood glucose levels, CRP and albumin levels, degree of malnutrition, steroid therapy, admission diagnosis, prior comorbidities, and the development of infectious complications during admission. However, the presence of diabetes or hyperglycemia before starting TPN was not associated with a greater mortality (Table 2) or a longer hospital stay. Furthermore, no differences were found for death or mean hospital stay between the patients with diabetes and those with hyperglycemia without diabetes. Of the 605 patients, 41 (6.9%) had blood glucose levels <70 mg/dL at some time; 57 (9.4%) received octreotide or somatostatin, and 13 (2.1%) received tacrolimus or cyclosporin. However, no association was found between the presence of hypoglycemia or treatment with octreotide, somatostatin, or immunosuppressive drugs and a greater risk of mortality. Furthermore, no significant differences were found in mortality according to the type of amino acids or lipids infused.

Table 3 summarizes the characteristics of the patients according to their mean capillary blood glucose levels (<140 mg/dL, 140–180 mg/dL, and >180 mg/dL) on all the days TPN was infused. Significant differences were found in age, BMI, total kilocalories given in the TPN, mean capillary blood glucose level, HbA_{1c}, SD of the capillary blood glucose levels, coefficient of variation of the blood glucose levels, CRP, units of insulin given per kilogram body weight, and type of insulin treatment used.

Table 4 shows the logistic regression data for the risk of in-hospital death. Age, CRP, SGA, mean blood glucose levels, grams of carbohydrate infused, admission diagnosis, and infectious complications all differed significantly after adjusting for the other variables.

CONCLUSIONS—The adjusted multivariate analysis of the data showed that an increased serum glucose level during infusion of TPN (mean values >180 mg/dL) is a risk factor for an increased risk of in-hospital death in noncritically ill patients. These findings confirm and widen the results of other studies because they were carried out at a single center with fewer patients and included retrospectively both ICU patients and mixed (3–6,8,11) or solely noncritically ill patients (9) or patients receiving allogeneic hematopoietic stem cell transplantation (7,10).

In the past, stress hyperglycemia often was believed to be a useful adaptive response, but hyperglycemia has been associated with increased mortality and morbidity in a variety of medical conditions and patient populations (19). This risk could be raised with effect from blood glucose levels above just 108–110 mg/dL (11,20). The patients in the present study with blood glucose levels >180 mg/dL had a 5.6 times higher risk of death than those having blood glucose levels <140 mg/dL. In addition, this trend toward greater mortality was also seen in patients with blood glucose levels of 140–180 mg/dL (losing significance after controlling for other variables).

The total number of grams of carbohydrates infused was associated with the risk of in-hospital death. The presence of diabetes, however, was not significant, as has been found in other studies (6,9,11), suggesting that hyperglycemia is the factor most contributing to the risk of complications and death. The HbA_{1c} also did not contribute significantly in the logistic regression model.

In the present study, we defined the presence of diabetes and hyperglycemia before TPN infusion not only from the chart data, but also from the laboratory findings. This approach gives more value to the data and could, in part, explain the differences in earlier studies, finding that the presence of diabetes sometimes increased (5) or did not increase (8,9,11) the risk for mortality. Indeed, the prevalence of diabetes may be greatly underestimated if it is based solely on the clinical history or chart data (21).

Hyperglycemia (chronic and acute) and insulin resistance could favor prothrombotic and proinflammatory alterations as well as increase oxidative stress and impair chemotaxis, leukocyte adhesion and transmigration, and complement activation (22). Clinically, the presence of hyperglycemia during TPN infusion has been associated with an increase in infectious complications in

Table 3—*Differences between subjects depending on mean capillary blood glucose level*

	Mean capillary blood glucose level			
Variable	<140 mg/dL	140–180 mg/dL	>180 mg/dL	*P* value
Patients	370 (61.2)	175 (28.9)	60 (9.9)	
Age (years)	61.1 ± 16.6	67.2 ± 13.4	65.1 ± 13.7	<0.001
Days hospitalized (*n*)	33.3 ± 27.7	33.5 ± 23.4	37.9 ± 30.6	NS
Days on TPN (*n*)	13.9 ± 11.6	12.1 ± 11.1	11.2 ± 7.1	0.08
BMI (kg/m^2)	24.6 ± 5.6	25.8 ± 5.2	27.3 ± 5.6	0.001
Total kilocalories administered through TPN	1,597 ± 324	1,655 ± 296	1,758 ± 354	0.001
Kilocalories/kg body weight	25.1 ± 5.3	25.0 ± 5.1	24.7 ± 4.0	NS
Total carbohydrates (g/kg)	3.7 ± 0.8	4.0 ± 0.9	3.5 ± 0.6	NS
Amino acids (g/kg)	1.27 ± 0.3	1.25 ± 0.2	1.26 ± 0.2	NS
Lipids (g/kg)	0.94 ± 0.2	0.96 ± 0.2	0.90 ± 0.2	NS
Capillary blood glucose mean (mg/dL)	119.0 ± 13.1	156.9 ± 11.6	224.6 ± 39.9	<0.001
HbA_{1c} (%)	5.5 ± 0.6	6.0 ± 0.8	6.9 ± 1.2	<0.001
Blood glucose SD	18.8 ± 8.1	33.8 ± 15.4	60.3 ± 27.5	<0.001
Coefficient of variation (%)	15.7 ± 6.3	21.4 ± 9.3	27.2 ± 11.8	<0.001
CRP level (mg/L)	84.6 ± 91.1	107.9 ± 104.1	124.5 ± 99.4	0.004
Albumin level (g/dL)	2.7 ± 0.6	2.7 ± 0.6	2.5 ± 0.6	0.07
Insulin units/kg body weight	0.07 ± 0.2	0.29 ± 0.5	0.60 ± 0.9	<0.001
Death	25 (6.8)	19 (10.9)	14 (23.3)	<0.001
Infectious complications	57 (15.4)	44 (25.1)	13 (21.7)	0.026
Type of insulin treatment used				
None	161 (43.5)	11 (6.3)	0 (0)	
Subcutaneous route (without intravenous insulin)	134 (36.2)	86 (49.1)	20 (33.3)	
Intravenous insulin (added to the TPN bag)	55 (14.9)	61 (34.9)	39 (65)	
Intravenous insulin infusion therapy	20 (5.4)	17 (9.7)	1 (1.7)	<0.001

Data are mean ± SD or *n* (%).

Table 4—*Logistic regression analysis: adjusted risk of death during hospitalization*

	B	Odds ratio	95% CI Lower	95% CI Upper	*P* value
Age	0.040	1.041	1.013	1.070	0.004
CRP level	0.004	1.004	1.001	1.007	0.05
Previous malnutrition (SGA)					
Normally nourished					0.12
Moderate malnutrition	0.55	1.73	0.62	4.86	0.29
Severe malnutrition	1.12	3.05	1.01	9.23	0.048
Mean blood glucose level during TPN					
<140 mg/dL					0.041
140–180 mg/dL	0.62	1.86	0.78	4.43	0.159
>180 mg/dL	1.72	5.60	1.47	21.39	0.01
Carbohydrates g/kg body weight	0.59	1.80	1.18	2.76	0.007
Diagnosis on admission					
Digestive					0.000
Surgery	–0.099	0.91	0.23	3.54	0.888
Oncology	1.89	6.63	1.64	26.83	0.008
Infectious disorders	0.51	1.67	0.31	9.07	0.551
Infectious complications during hospitalization	1.38	3.98	1.87	8.45	0.000

Also included in the model but without statistical significance were sex, diabetes status before TPN, use of corticosteroids, blood glucose variability (SD), glycated hemoglobin, insulin units/kg body weight, presence of comorbidity before TPN, and albuminemia.

some studies (5,6,8) but not all (3,9–11). Moreover, the use of intensive insulin therapy in noncritically ill patients seems to reduce the risk of infections (23). In the present study, the incidence of infectious complications was greater in patients with higher mean blood glucose values and in those who died, strengthening the idea of the role of these complications in outcome and mortality.

In humans, van Der Voort et al. (4) found that even low amounts of infused glucose were associated with increased mortality when glucose levels were not controlled. Part of the disparity between the results in the different papers on intensive treatment in ICU patients (19,24,25) could be the result of the nutritional therapy used in the different studies.

Hypoglycemia is the most common complication associated with inpatient insulin therapy, and it could increase mortality (26). In the present study, the prevalence of hypoglycemia was very low, and in fact, it was not associated with worse outcomes. The fact that the patients were not critically ill (less severe), that the patients started from a low baseline HbA_{1c} (even the diabetic patients), and the mode of delivery of the insulin (mostly in the bag or subcutaneously) may have influenced the results.

Glycemic variability has been suggested to be a significant independent predictor of ICU and hospital mortality (27,28). The SD in the present study was higher in patients who died, although the association lost significance after correcting for the other variables in the multivariate model. Although the variability is a factor that can contribute to the prognosis of these patients, hyperglycemia per se would appear to be the most contributing factor in noncritically ill patients receiving TPN.

Because the present sample comprised a heterogeneous population of noncritically ill patients from different centers, we used as markers of severity the measurement of CRP and albumin levels, which are also associated with worse outcomes and mortality in inpatients receiving artificial nutrition (29). As expected, the albumin levels were lower and the CRP levels higher in the patients who died, and CRP levels were higher in relation to blood glucose control. After adjusting for other variables, CRP level still contributed significantly in the multivariate model, strengthening the possible role of inflammation and the severity of the underlying disorder on complications and mortality in noncritically ill patients receiving TPN.

Malnutrition is associated with worse outcomes in hospitalized patients (1,30) and, therefore, could be an important confounding factor when interpreting the results of other studies that either failed to evaluate it or just included the BMI (4–6,8–11). The SGA is a simple method, and it has been used in many studies to predict adequately morbidity and mortality in hospitalized patients (16,31). In the present study, the risk of dying was three times greater in the severely malnourished patients compared with the normally nourished patients. Malnutrition together with hyperglycemia could be one of the most conditioning factors related to poor prognosis.

The use of special amino acid (e.g., enriched with glutamine) or lipid (based on olive oil or supplemented with omega-3 fatty acids) formulas may be beneficial to prevent or treat hyperglycemia (32,33), and the use of steroids could increase it (34), possibly increasing morbidity and mortality. We found no differences that depended on the type of macronutrient used, although the patients in the present series who received corticosteroids experienced greater mortality; nevertheless, this association was not significant in the multivariate analysis. The presence of accompanying diseases before hospital admission was a condition of in-hospital mortality, as in other studies (11).

The present study is not exempt from limitations. First, the blood samples were not centralized or the same blood glucose monitor was not used, which could contribute to small under- or overestimates of the real blood glucose values. Second, apart from infections, no other complications were recorded during the admission. Third, we did not establish a causal relation between capillary blood glucose levels on admission and mortality.

In conclusion, the results show that hyperglycemia in noncritically ill patients receiving TPN is associated with increased in-hospital mortality. The data suggest that the goal of metabolic control in noncritically ill patients (with or without diabetes) receiving TPN should be to reach a mean blood glucose level of <180 mg/dL. This study opens the door to further prospective studies in noncritically ill patients to determine whether stricter blood glucose control during TPN infusion improves the outcome for the patients and reduces mortality.

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