Original Article

Glycemic Variation in Tumor Patients with Total Parenteral Nutrition

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Abstract

Background: Hyperglycemia is associated with poor clinical outcomes and mortality in several patients. However, studies evaluating hyperglycemia variation in tumor patients receiving total parenteral nutrition (TPN) are scarce. The aim of this study was to assess the relationship between glycemia and tumor kinds with TPN by monitoring glycemic variation in tumor patients.
Methods: This retrospective clinical trial selected 312 patients with various cancer types, whose unique nutrition treatment was TPN during the monitoring period. All patients had blood glucose (BG) values assessed at least six times daily during the TPN infusion. The glycemic variation before and after TPN was set as the indicator to evaluate the factors influencing BG.
Results: The clinical trial lasted 7.5 ± 3.0 days adjusted for age, gender, family cancer history and blood types. There were six cancer types: Hepatic carcinoma (HC, 21.8%), rectal carcinoma (17.3%), colon carcinoma (CC, 14.7%), gastric carcinoma (29.8%), pancreatic carcinoma (11.5%), and duodenal carcinoma (DC, 4.8%). The patients were divided into diabetes and nondiabetes groups. No statistical differences in TPN glucose content between diabetes and nondiabetes groups were found; however, the tumor types affected by BG values were obvious. With increasing BG values, DC, HC and CC were more represented than other tumor types in this sequence in diabetic individuals, as well as in the nondiabetic group. BG was inclined to be more easily influenced in the nondiabetes group. Other factors did not impact BG values, including gender, body mass index, and TPN infusion duration time.
Conclusions: When tumor patients are treated with TPN, BG levels should be monitored according to different types of tumors, besides differentiating diabetes or nondiabetes patients. Special BG control is needed for DC, HC and CC in both diabetic and nondiabetic patients. If BG overtly increases, positive measurements are needed to control BG values. The ClinicalTrials.gov ID is NCT02024321.

Key words: Blood Glucose; Total Parenteral Nutrition; Tumor Patients

Introduction

Hyperglycemia is a common adverse outcome in critically ill patients; it is associated with high mortality rates and occurs in individuals with and without a previous history of diabetes.[1-3] In addition, glucose is the main energy source for cancer cells, with the long hyperglycemic state providing a nutrition base to promote cancer cell differentiation and growth.[4] As a means of nutrition supply, especially for abdominal surgery patients, total parenteral nutrition (TPN) prevents nutrition loss after surgery, and improves survival rate and quality of life.[5,6]

In 2005, Cheung *et al*.[2] reported that hyperglycemia is a predictor of poor outcomes in TPN. The confirmation of a relation between blood glucose (BG) levels and adverse outcomes supports a tight glycemic control in these patients.

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In 2010, Pasquel *et al*.[7] collected the BG data in three parts, that is, pre-TPN (before 24 h), within 24 h, and during days 2–10 of TPN for patients, for 1 year, and concluded that hyperglycemia is associated with increased hospital complications and mortality. They also pointed out that BG values pre-TPN and within 24 h of initiation of TPN are better predictors of hospital mortality and complications compared with the mean BG level during the entire duration of TPN.

Therefore, how the BG fluctuates in various types of the tumor with TPN is an open question. Another unanswered question concerns the factors that influence BG under TPN. To the best of our knowledge, no report regarding the relations of BG with different tumor types in patients receiving TPN has been published. To address these questions, we performed a retrospective study to determine the relations among these factors in tumor patients.

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Methods

We performed a retrospective case-control study to assess tumor patients in Cancer Hospital/Institute, Chinese Academy of Medical Sciences, from January 2013 to December 2014 to evaluate the effect of TPN on BG after surgery. Tumor patients entered the study on the 1st day of TPN infusion, and BG values were recorded at least every 6 times per day after TPN infusion. The study was approved by the Ethics Committee of Cancer Hospital/Institute, Chinese Academy of Medical Sciences, and written informed consent was obtained from each patient.

Data collection

Inclusion criteria

This work involved surgery patients receiving TPN during the calendar year of 2013 and 2014 in Cancer Hospital/Institute, Chinese Academy of Medical Sciences.

Exclusion criteria

Patients were excluded with one of these criteria: (1) TPN not being the unique nutrition source; (2) TPN duration shorter than 2 days; (3) use of anti-tumor drugs after surgery; (4) no surgery.

Total parenteral nutrition scheme

Therapeutic schemes: For tumor patients, a transfusion apparatus was applied and nutrients were delivered intravenously through the central venous catheter 18–20 h/d, with a transfusion speed of 1–2 $ml \cdot kg^{-1} \cdot d^{-1}$.

Blood glucose detection

The One Touch Ultra Vue glucometer (Johnson and Johnson, USA) was used to collect BG levels 6 times per day (interval survey 6 h during each time) during the whole TPN infusion. The average BG values within 24 h were considered BG levels for a giving day.

Data analysis

Blood glucose levels were divided into three parts: Pre-TPN, within 24 h, and 2–10 days after 24 h.

Two-sample Wilcoxon's tests were used to compare the demographic and clinical characteristics between diabetic and nondiabetic groups. Analyses were carried out with SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Pictures were drawn with Microsoft Excel Professional 2013. A $P < 0.05$ was considered to be statistically significant.

Results

Demographic characteristics are summarized in Table 1. A total of 312 patients averaging 58.6 ± 11.1 years, including 61.9% men (body mass index [BMI], 24.2 ± 3.6 kg/m^2). There were 25.3% known diabetic patients. All individuals received TPN after surgery with a mean duration of 7.5 ± 3.0 days. Six tumor types were selected: Hepatic carcinoma (HC, 21.8%), rectal carcinoma (RC, 17.3%), colon carcinoma (CC, 14.7%), gastric carcinoma (GC, 29.8%), pancreatic carcinoma (PC, 11.5%), duodenal carcinoma (DC, 4.8%).

Table 1: Main characteristics of tumor patients

Items	Diabetic patients (*n*=79)	Nondiabetic patients (*n*=233)	*P*
Male, *n* (%)	50 (63.2)	143 (61.4)	0.79
Age, years	61.4 ± 8.0	57.7 ± 11.8	<0.01
BMI, kg/m^2	24.53 ± 3.66	24.14 ± 3.58	0.41
Family cancer history, *n* (%)	16 (20.3)	39 (16.7)	0.50
Tobacco and alcohol addiction, *n* (%)	25 (31.6)	61 (26.2)	0.38
Hypertension, *n* (%)	37 (46.8)	57 (24.5)	<0.001
Blood types, *n*	A: 30, AB: 4, B: 26, O: 19	A: 77, AB: 20, B: 66, O: 70	0.47

BMI: Body mass index.

Table 2: Mean BG values in different periods, mmol/L

Time	Diabetic group (*n*=79)	Nondiabetic group (*n*=233)	*P*
Pre-TPN	8.22 ± 2.40	5.41 ± 1.32	<0.001
Within 24 h	12.10 ± 3.23	10.16 ± 2.63	<0.001
After 24 h	11.01 ± 2.20	8.36 ± 2.00	<0.001

BG: Blood glucose; TPN: Total parenteral nutrition.

The mean BG level during TPN was 9.2 ± 2.2 mmol/L; it was 6.1 ± 2.1 mmol/L before TPN and increased to 10.7 ± 2.9 mmol/L within 24 h. Interestingly, mean BG levels returned to 9.0 ± 2.4 mmol/L from 24 h till the end of the TPN infusion.

As BG levels are greatly influenced by diabetes in patients [Table 2], the master sample was divided into two groups, including diabetic and nondiabetic patients. Therefore, all subsequent comparisons were based on these two subgroups to avoid the diabetes factor.

Total parenteral nutrition infusion patients were divided into two groups respectively, according to insulin usage status or diabetes disease. The *F*-test indicated no statistical difference in TPN glucose content between groups.

In the diabetic group, BG levels in HC patients varied considerably, and highest values were obtained for all tumor kinds. BG variations in PC patients were the least, with minimal change within 24 h; meanwhile, the changes in DC were the most pronounced. Variations of BG levels in CC patients were close to those of GC and RC, and values were very small. In the nondiabetic group, BG values and variations in DC patients were the highest. HC value increased greatly as well.

Tumor types

With increasing BG values, DC, HC and CC were more represented than other tumor types in this sequence in diabetic individuals, as well as in the nondiabetic group. Both the increasing and decreasing BG ranges in DC and HC were large in the two subgroups. For patients with decreasing BG range after 24 h, all tumor types decreased faster in the nondiabetic group compared with diabetic individuals. Decreasing BG ranges in DC, CC and GC were higher than those obtained for the other

three tumor kinds. In the nondiabetic group, BG levels in HC patients increased rapidly and decreased slowly. Remarkably, decreasing ranges in RC and PC were not obvious compared to other cancer types [Figure 1, Table 3]. Therefore, it is necessary to control BG in DC patients. In diabetic patients, special attention is needed for those with

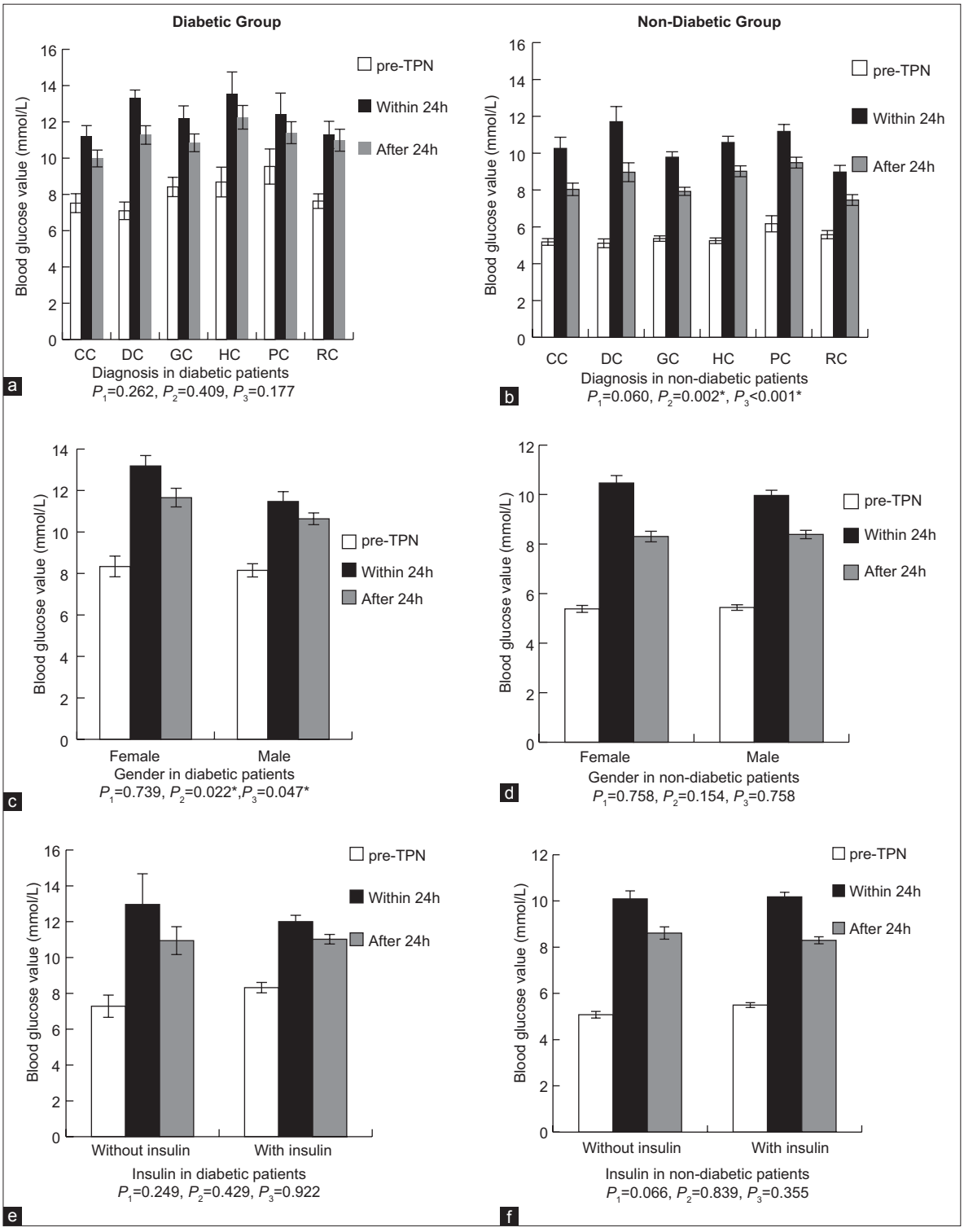

Figure 1: Blood glucose value variations with different impacting factors (mean ± SE). Diagnosis (a), gender (c), insulin (e), BMI (g) and TPN duration (i) in diabetic patients. Diagnosis (b), gender (d), insulin (f), BMI (h) and TPN duration (j) in nondiabetic patients. HC: Hepatic carcinoma; CC: Colon carcinoma; DC: Duodenal carcinoma; GC: Gastric carcinoma; PC: Pancreatic carcinoma; RC: Rectal carcinoma. *P* value is the result of comparing the mean value in each stage. *P* value is calculated from one-way ANOVA. *$P < 0.05$. P_1: Blood glucose levels pre-TPN; P_2: Blood glucose levels within 24 h of TPN (within 24 h); P_3: Blood glucose levels after during TPN infusion after 24 h (After 24 h).

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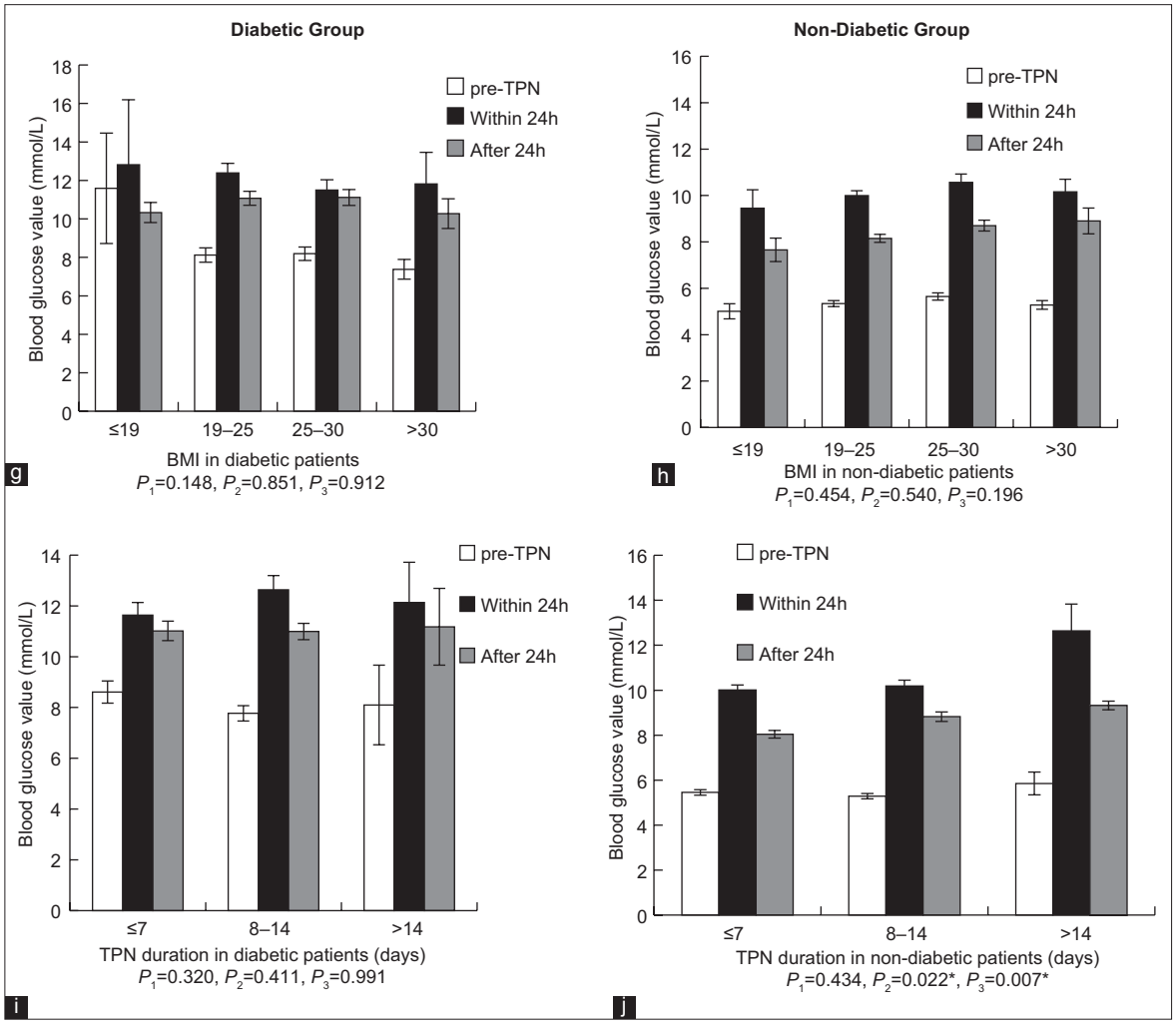

Figure 1: Contd...

HC, GC and CC at the beginning of the TPN infusion, and RC and PC patients during prolonged TPN infusion. In the nondiabetic group, attention should be paid to HC patients in both stages of TPN infusion.

In the diabetic group, BG in female rose higher after TPN infusion while no difference occurred in the nondiabetic group. There was no BG value difference in Insulin infusion and personal BMI index in the two groups. In the diabetic group, the BG increased after TPN, no difference appearing in longer usage, but the longer using TPN, the higher BG level in nondiabetic group [Figure 1].

Blood glucose levels were affected by tumor kind and insulin; consequently, the results in Figure 1 were further analyzed in Figure 2, to discuss the two factors separately. Here, we chose patients as a control group, who were confirmed as noncancer patients after surgery [Figure 2]. BG values were calculated as the averages obtained during the monitored periods.

In diabetic patients group, though without distinct differences, BG variation had its own characteristics in kinds of tumor. In nondiabetic patients group, BG level rose distinctly after TPN infusion (see the *P* value under the pictures); furthermore, there was more distinct difference in different kinds of tumor without any insulin [Figure 2d]. The influence from various tumor types was as follows:

- Hepatic carcinoma: As shown in Figure 2, BG levels in HC patients were high, with or without insulin in the diabetic group. It was also high and showed a large variation (increasing and decreasing range) in the nondiabetic group; the decline range was not the same as with other cancer types [Figure 2d.] after 24 h. These data indicated that BG levels in HC patients were greatly influenced by TPN.
- Colon carcinoma: Its BG level changed overtly in the diabetic group [Figure 2b]. The increasing BG range was even higher than that of HC; however, absolute BG values were low as shown in Figure 2a, and its variation high [Figure 2c]. This suggested the necessity to control BG levels in CC with insulin in the diabetic group.
- Rectal carcinoma: No distinct changes in the four sub-groups and absolute values were low in the subgroups. The change ranges were similar [Figure 2b-2d]. The only difference was that decreasing BG range after 24 h was not so obvious [Figure 2a], indicating that extra BG control is needed in this situation.

Table 3: *P* value and corresponding *F* value in Figure 1

Items	Diabetic group (*n*=79)		Nondiabetic group (*n*=233)	
	P	*F*	*P*	*F*
Diagnosis				
Pre-TPN	0.262	1.328	0.060	2.160
Within 24 h	0.409	1.025	0.002*	3.967
After 24 h	0.177	1.577	<0.001*	6.038
Gender				
Pre-TPN	0.739	0.112	0.758	0.095
Within 24 h	0.022*	5.484	0.154	2.047
After 24 h	0.047*	4.094	0.758	0.095
Insulin				
Pre-TPN	0.249	1.352	0.066	3.423
Within 24 h	0.429	0.631	0.839	0.041
After 24 h	0.922	0.010	0.355	0.859
BMI				
Pre-TPN	0.148	1.751	0.454	0.919
Within 24 h	0.851	0.338	0.540	0.778
After 24 h	0.912	0.245	0.196	1.523
TPN duration				
Pre-TPN	0.320	1.156	0.434	0.839
Within 24 h	0.411	0.900	0.022*	3.893
After 24 h	0.991	0.009	0.007*	5.015

TPN constituents: Medium and long chain fat emulsion (20%, 500 ml); compound amino-acids (8.5%, 400 ml), decavitamin (10 ml, Vitamin A: 2500 IU, Vitamin D2: 200 IU, Vitamin E: 15 mg, Vitamin K: 2 ml); Micronutrient (10 ml, chromium chloride: 53.3 μg, copper chloride: 3.4 mg, ferric chloride: 5.4 mg, manganese chloride: 0.99 mg, sodium molybdate: 48.5 μg, zinc chloride: 13.6 mg, sodium fluoride: 2.1 mg); concentrated sodium chloride (10%, ca 40 ml); potassium chloride (3.0 g, 30 ml); sodium glycero-phosphate (10 ml, 2.16 g); glucose injection (50%, 250 ml); insulin (ca 30 IU); glucose injection (10%, 1000 ml); glucose and sodium chloride injection (500 ml: 5% glucose, 0.9% sodium chloride).

- Duodenal carcinoma: BG levels in DC patients rose highest in four subgroups; hence, it is necessary to strengthen BG control in DC patients, e.g., increasing insulin dose and decreasing glucose content.
- Gastric carcinoma: No distinct variation was observed for the four sub-groups. Absolute values within 24 h were high [Figure 2a].
- Pancreatic carcinoma: As shown in Figure 2a, its increasing range was as high as that of HC: Similar features were obtained as in Figure 2c and 2d.
- Other factors: Hypertension, family cancer history, tobacco and alcohol habits and blood types showed no overtly different effect on BG in either sub-group.

Discussion

Diabetes is associated with an increased risk of developing cancer and dying from it.[8] Both observational and laboratory studies have provided evidence that impaired metabolism, obesity, hyperglycemia and hyperinsulinemia may have a role in cancer development, progression and prognosis. Besides, culture of breast cancer MCF-7 cells in hyperglycemia significantly promotes the motile activity in comparison to the normal physiological glucose level.[9]

Diabetes may directly promote the progression of PC by pancreatic duct enlargement and hypertension, as well as enabling an increased tumor volume. Hyperglycemia may be the first clinical manifestation and is helpful in the early diagnosis of PC. Furthermore, antidiabetic drugs can have different effects on the occurrence and prognosis of PC.[10] Possible mechanisms for increased cancer risk in diabetes include cellular proliferative effects of hyperglycemia, hyperinsulinemia, and abnormalities in insulin/insulin-like growth factor (IGF) receptor pathways.[11] Other potential mechanisms include increased circulating, local or bioavailable IGF-1, hyperglycemia, dyslipidemia, increased circulating or local estrogen, adipokines, and direct and indirect effects of inflammatory cytokines.[12] The risk of developing PC can be reduced by aggressive prevention and treatment of T2DM and obesity, and the prompt diagnosis of T3cDM may allow detection of a tumor at a potentially curable stage.[11]

Hyperglycemia may have direct effects on the tumor site, or indirect effects through soluble factors. Direct effects promote: (i) Increased growth factor signaling and accelerated cell cycle. (ii) an initial accumulation of reactive oxygen species (ROS) enhances mutagenesis and leads to the secondary selection of clones with diminished ROS production to ensure survival. Alternatively, some cancer cells also export ROS to neighboring cells to ensure their own survival. (iii) the upregulation of chemo-attractants for invasion, such as glial cell line-derived neurotrophic factor. (iv) an increase in the WNT/b-catenin signaling pathway, which favors proliferation, antisenescence and invasion. Indirect effects of hyperglycemia on cancer cells are mediated through (i) increased levels of insulin/IGF-1 and/or (ii) inflammatory cytokines as well as (iii) a diminished immunological surveillance. The reduced immune response is achieved through the reduction in ascorbic acid transport in critical immune cells that diminishes their phagocytic and proliferation capabilities. Both direct and indirect effects converge on cancer hallmarks (increased proliferation, survival, invasion, and migration and accumulation of mutations in the DNA).[13]

Recent data showed that diabetes may negatively impact both cancer risks and treatment outcomes. It is important to identify patients at risk for complications that arise from cancer treatment in the setting of preexisting diabetes. In addition, underlying hyperglycemia or hidden diabetes in a patient undergoing cancer treatment such as chemotherapy, including steroid administration, and TPN should be identified and managed.[14] When TPN is used, BG levels should be kept under 150 mg/dl (8.33 mmol/L) by pertinently administering insulin or limiting glycemic intake.[15]

Blood glucose levels are influenced by tumor types when TPN is used. Each tumor kind affects BG levels differently. Moreover, BMI, and hypertension, among other factors, do not influence BG levels in a statistically significant manner.

In summary, our study reveals the relationship between BG values and different tumors types with TPN in three

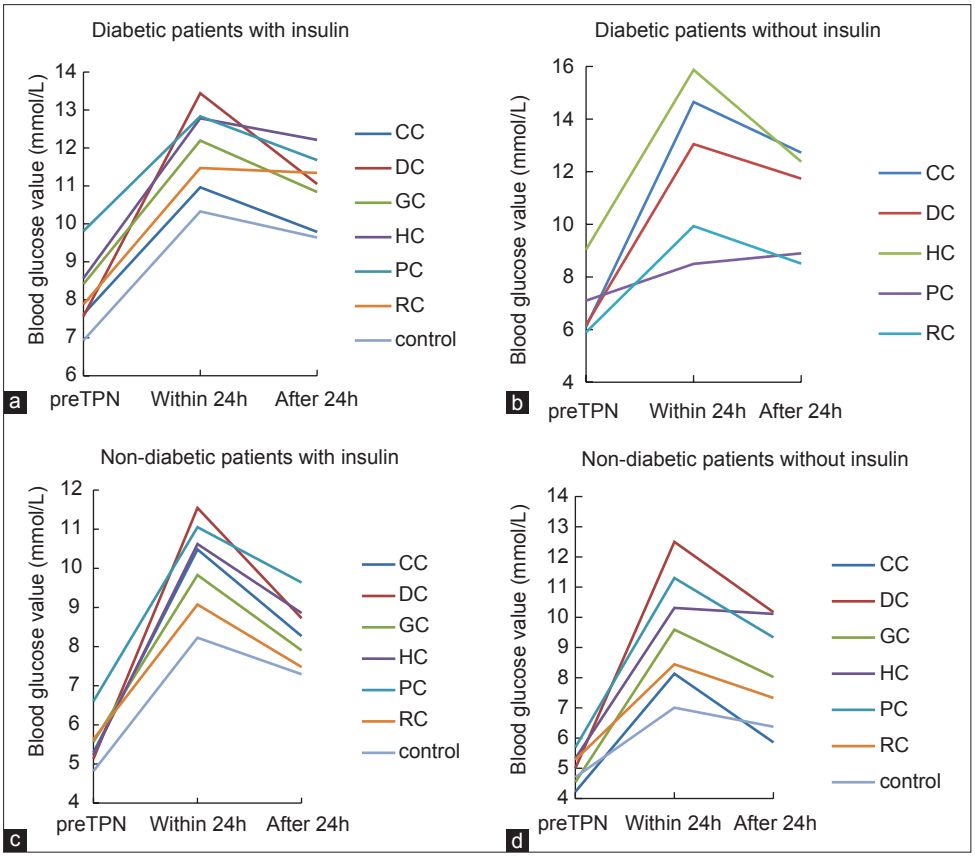

Figure 2: Blood glucose values in diabetic and nondiabetic groups with or without insulin. Blood glucose values increases highly within 24 h and decreases after 24 h; however, the last values are higher than those obtained pre-TPN. Blood glucose levels in DC are highest in Figure 2a, 2c and 2d. Blood glucose levels in HC are highest in Figure 2b. HC: Hepatic carcinoma; CC: Colon carcinoma; DC: Duodenal carcinoma; GC: Gastric carcinoma; PC: Pancreatic carcinoma; RC: Rectal carcinoma.

stages (pre-TPN, within 24 h and 2–10 days after 24 h). Our findings indicate the necessity to separate patients by tumor types and control BG levels in the correct setting, besides taking into account the diabetic and nondiabetic condition. Special BG control is needed for DC, HC and CC patients, in both the diabetic and nondiabetic groups. Work is in progress assessing the mechanisms by which tumor types affect BG.

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