Original Article

Metabolic changes in patients using total parenteral nutrition

Alterações metabólicas em pacientes em uso de nutrição parenteral total

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ABSTRACT

Introduction: Total parenteral nutrition (TPN) is a type of nutrition administered intravenously and is used when the gastrointestinal tract is non-functional or another dietary route is not sufficient to guarantee the necessary nutritional intake for the individual. Its use can be associated with some metabolic alterations when related to calorie overload from the glucose and lipids present in these formulas. Other changes may be related to a drop in electrolytes, indicative of refeeding syndrome. With this in mind, this study aims to investigate the association between the use of parenteral nutrition and possible metabolic alterations. **Methods:** Data were collected using a standardized questionnaire, where part of the data was collected through an interview with the patient and the other part was obtained from the electronic medical record. Data analysis was carried out using the statistical program Stata®. **Results:** The majority of patients were male, with a mean age of 58 years. The main diagnoses were pancreatitis and gastric adenocarcinoma. The average duration of PTN use was 8 days. During the study, 75% of patients had inadequate calorie intake. Out of these, 50% of them had a higher calorie intake than the calculated target and 25% lower. The main metabolic alterations observed were hyperglycemia, hypokalemia, hypertriglyceridemia, hypophosphatemia and hypernatremia. When correlating the time of use of NPT and the metabolic alterations elucidated, hypophosphatemia was the main finding of the study ($p<0.005$). **Conclusion:** Patients on TPN with calorie overload at the start of nutritional therapy may present electrolyte, glycemic and liver marker alterations.

RESUMO

Introdução: A nutrição parenteral total (NPT) é um tipo de nutrição administrada por via endovenosa e é utilizada quando o trato gastrointestinal se encontra não funcionante ou outra via alimentar não é suficiente para garantir o aporte nutricional necessário para o indivíduo. A sua utilização pode ser associada a algumas alterações metabólicas quando relacionadas à sobrecarga calórica, advinda de glicose e lipídeos presentes nessas fórmulas. Outras alterações podem estar relacionadas à queda de eletrólitos indicativos de síndrome de realimentação. Com isso, o presente estudo visa investigar a associação entre o uso de nutrição parenteral e possíveis alterações metabólicas. **Método:** Os dados foram coletados utilizando um questionário padronizado, onde parte dos dados foi coletada por meio de entrevista com o paciente e a outra parte dos dados obtida pelo prontuário eletrônico. A análise de dados foi realizada pelo programa estatístico Stata®. **Resultados:** A maioria dos pacientes era do sexo masculino, com idade média de 58 anos. Os principais diagnósticos foram pancreatite e adenocarcinoma gástrico. O tempo médio de uso da NPT foi de 8 dias. Durante o estudo, 75% dos pacientes apresentaram oferta calórica inadequada. Desses, 50% apresentaram oferta calórica inadequada superior à meta calculada e 25% inferior. As principais alterações metabólicas observadas foram hiperglicemia, hipocalemia, hipertrigliceridemia, hipofosfatemia e hipernatremia. Correlacionando o tempo de uso de NPT e as alterações metabólicas elucidadas, a hipofosfatemia foi o principal achado do estudo ($p<0,005$). **Conclusão:** Pacientes em uso de NPT com sobrecarga calórica no início da terapia nutricional podem apresentar alterações eletrolíticas, glicêmicas e de marcadores hepáticos.

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INTRODUCTION

Total parenteral nutrition (TPN) is an intravenously administered solution that provides macro and micronutrients[1-4]. It is mainly used when the gastrointestinal tract is obstructed, when it is not possible to use it or when another feeding route, oral or enteral, cannot be used or is insufficient[5-7].

At the beginning of the use of TPN, they were formulas rich in glucose, and for this reason, hyperglycemia was the most common adverse effect. In order to reduce its occurrence, less dense and safer lipid emulsions were created, reducing the amount of soybean oil and adding medium-chain triglycerides (MCT) and omega-3 (w-3) to provide energy[6,8].

Formulations can be manipulated or industrialized. The current industrialized formulas are composed of: glucose; amino acids; lipid emulsions, in some formulas only soybean oil and in others added w-3, TCM, omega-9 (w-9), and electrolytes. As such, it is necessary to to supplement vitamins and trace elements[2-4]. Manipulated parenteral nutrition, on the other hand, is where the amount of each nutrient is individualized in the bag according to each patient's needs[9].

Among the possible metabolic alterations found in the use of NP, there are: glycemic alterations, alterations in the lipid profile, liver dysfunction (including GOT: glutamic oxalacetic transaminase; GPT: glutamic pyruvic transaminase; GAMMA-GT: gamma glutamyl transferase and AP: alkaline phosphatase), electrolyte alterations (sodium, potassium, phosphorus and magnesium) and refeeding syndrome[8,10-12].

Refeeding syndrome is described as a hormonal-metabolic disorder characterized by very rapid or excessive feeding in the first 7 days of feeding or return to feeding, whether orally, enterally or parenterally, both in severely fasted patients and those with risk factors for the syndrome. It is manifested by hypophosphatemia, hypokalemia, hypomagnesemia, hyponatremia and water imbalance[8,12]. It can happen because, during fasting, blood glucose and insulin decrease and glucagon increases. This makes it necessary to use reserves of lipids and proteins as a source of energy, reducing the basal metabolic rate and configuring a catabolic state. As a result, the body uses autophagy to maintain depleted intracellular electrolyte stores, but extracellular electrolytes are not always depleted or diminished. After food is reintroduced, catabolism is reversed to anabolism, with a spike in insulin that carries electrolytes and thiamine into the cell, reducing serum levels[13].

The main reasons for the negative outcomes associated with the use of PN are mainly related to overfeeding and complications arising from the underlying disease[6,14-15].

The purpose of this study is to investigate the association between the use of parenteral nutrition and possible metabolic alterations, and to analyze whether there is a correlation between the time of use of TPN, metabolic alterations and calorie and protein adequacy.

METHOD

This is a cross-sectional study carried out in the wards and intensive care units (ICU) of a public hospital in the center-west of Brazil. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[16]. Data was collected between October 2023 and June 2024. The sample was conducted by convenience.

The inclusion criteria were patients over the age of 18 and using TPN exclusively. The exclusion criteria were: patients who did not have a request for a triglyceride (TG) test, those who already had hypertriglyceridemia on admission (TG >150 mg/dl), patients who did not sign the informed consent form (ICF) and patients who started another route while using PN.

Patients were tracked based on the report of patients using parenteral nutrition in the electronic medical record. Sociodemographic data was collected by interviewing the patient or the family member/accompanying person when the patient was not conscious and oriented to do so. The parenteral formula was selected by the nutrologist and prescribed in the electronic medical record, and its nutritional composition was obtained from the manufacturer's information.

The weight and height used to monitor the adequacy of the nutritional goal were collected from the patient at the time of the interview, along with the arm circumference (AC), calf circumference (CC), and knee height (KH). For patients who were unable to report their weight, the Chumlea formula was used[17]. Hemoglucotests (HGTs) were collected to monitor blood glucose on a daily basis, with times according to the doctor's prescription. For these patients, records ≥181 mg/dl were considered hyperglycemia, according to the ASPEN guidelines for hospitalized patients[18].

The biochemical tests were obtained from the unit's laboratory system with their respective reference values. Biochemical tests for monitoring TPN were requested on day zero of nutritional therapy and every 7 days after its start, according to the unit's standardized protocol. The biochemical tests for GOT, GPT, GAMMA-GT and AP were grouped together and presented as liver alterations. The existence of liver alterations was confirmed in any patients which presented alterations in any of these exams. The tests were evaluated between the 1st and 10th day of TPN.

The calorie and protein targets were calculated by the nutrologist according to the specific characteristics and stage of each patient's illness.

The study was approved by the Research Ethics Committee of the Hospital de Urgências de Goiás, GO, Brazil, under opinion number 73820523.2.0000.0033, and is in accordance with Resolution 466/12 of the National

Health Council. The research complies with the General Data Protection Law.

Statistical analysis was carried out using the software Stata (StataCorp LLC, version 15.0, College Station, USA). Initially, a descriptive analysis was carried out, where categorical variables were presented in absolute and relative frequencies. For continuous variables, measures of central tendency and dispersion were calculated, as appropriate, based on the results of the Shapiro-Wilk normality test. When the distribution of continuous variables was considered normal ($p>0.05$), the data was presented as mean and standard deviation (SD). On the other hand, for variables that did not show a normal distribution ($p\leq0.05$), the median and interquartile ranges (IQ) were used.

To assess the association between metabolic alterations and the length of time using parenteral nutritional therapy (TPN), the Mann-Whitney U test was applied, as this was a non-parametric method suitable for comparing two independent samples. This test was chosen due to the non-parametric nature of the dependent variable (time on NPT). Values of $p<0.05$ were considered statistically significant.

RESULTS

The study investigated 38 patients using TPN. After applying the inclusion and exclusion criteria, a final sample of 14 participants was obtained. Details of the sample composition are shown in Figure 1.

The majority of patients were male (78.6%) and the mean age was 58.4±15.2 years. The median BMI was 22.7 kg/m^2 (IQR = 21.5-30.5 kg/m^2), while the mean AC and CC were 29.8±4.6 cm and 34.0±4.1 cm, respectively. The most prevalent comorbidities were hypertension (35.7%) and diabetes (21.4%). The location of patients was numerically the same: 50% were in the ward and 50% in the ICU. The median duration of use of TPN was 8 days (IQ: 3-14 days). The main indications for the use of PN varied, the most prevalent being pancreatitis (14.3%) and gastric adenocarcinoma (14.3%) (Table 1).

Table 1 – Characterization of the sample of patients using parenteral nutritional therapy in an emergency hospital in Goiânia, GO, Brazil (2024).

Variables	Total sample (n=14)
Sex, n (%)	
Male	11 (78.6)
Female	3 (21.4)
Age (years), mean +SD	58.4±15.2
BMI (kg/m^2), median (IQ)*	22.7 (21.5–30.5)
AC (cm), mean + SD**	29.8 ±4.6
CC (cm), mean + SD**	34.0 ±4.1
Diabetic, n (%)	
No	11 (78.6)
Yes	3 (21.4)
Hypertension, n (%)	
No	9 (64.3)
Yes	5 (35.7)
Service location, n (%)	
Ward	7 (50.0)
ICU	7 (50.0)

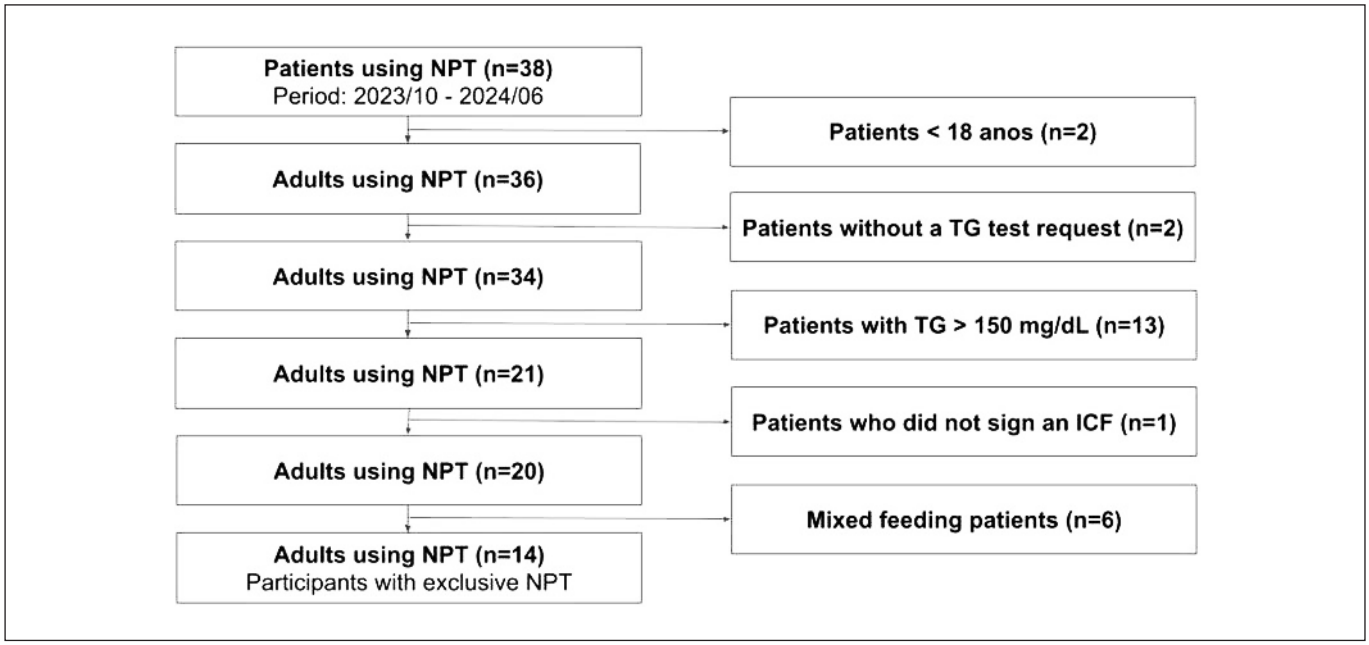

Figura 1 *- Processo de amostragem do estudo por meio dos critérios de inclusão e exclusão.*
TPN = total parenteral nutrtion; ICF = informed consent form; TG = triglycerides; n = samepl size.

Continuation Table 1 – Characterization of the sample of patients using parenteral nutritional therapy in an emergency hospital in Goiânia, GO, Brazil (2024).

Variables	Total sample (n=14)
Time spent using NPT (days), median (IQ)	8 (3-14)
NPT Indication, n (%)	
Cholelithiasis	1 (7.1)
Multiple organ damage***	1 (7.1)
Enteric injury****	1 (7.1)
Pancreatitis	2 (14.3)
Gastric adenocarcinoma	2 (14.3)
Perforated ulcer	1 (7.1)
Ischemia	1 (7.1)
Esophageal necrosis	1 (7.1)
Duodenal stenosis	1 (7.1)
Intestinal neoplasm	1 (7.1)
Esophageal varices	1 (7.1)
Diverticulitis Hinchey IV	1 (7.1)

AC = arm circumference; CC = calf circumference; SD = standard deviation; IQ = interquartile range; BMI = body mass index; TPN = total parenteral nutrition; ICU = intensive care unit; n = sample size; * = data missing for 2 males; ** = missing for 2 males and 1 female; *** = spleen, pancreas and intestine (site of intestine not specified); **** = unspecified location of the intestine.

With regard to calorie adequacy, 75% of patients did not reach the calculated calorie target (in kcal/kg/day). Among these, 25% received calories below the recommended level, and 50% received calories above the recommended level. Protein adequacy (in g/kg/day) was reached in 50% of patients. All the patients who didn't reach the target received a lower amount of protein than recommended (Table 2).

Table 2 – Caloric-protein adequacy of parenteral nutritional therapy in patients using parenteral nutritional therapy at an emergency hospital in Goiânia, GO, Brazil (2024).

Adequacy	Calories (kcal/kg/day) n (%)	Protein (g/kg/day) n (%)
Achieved	3 (25.0)	6 (50.0)
Not achieved	9 (75.0)	6 (50.0)
Lower	3 (25.0)	6 (50.0)
Higher	6 (50.0)	0 (-)

2 patients did not have calorie and protein targets calculated; n = sample size.

The main alterations observed were hyperglycemia (71.4%), hypokalemia (63.6%), hypertriglyceridemia (57.1%), hypophosphatemia (45.5%), and hypernatremia (42.9%). Hepatic alterations were found in 41.7% of patients. Hyponatremia was less common, affecting only 14.3% of patients, while hypomagnesemia occurred in 36.4% of them (Table 3).

Table 3 – Prevalence of metabolic alterations in patients using parenteral nutritional therapy at an emergency hospital in Goiânia, GO, Brazil (2024).

Metabolic changes	No n (%)	Yes n (%)
Liver changes	7 (58.3)	5 (41.7)
Hyperglycemia	4 (28.6)	10 (71.4)
Hypoglycemia	11 (78.6)	3 (21.4)
Hypokalemia	4 (36.4)	7 (63.6)
Hypernatremia	8 (57.1)	6 (42.9)
Hyponatremia	12 (85.7)	2 (14.3)
Hypophosphatemia	6 (54.5)	5 (45.5)
Hypertriglyceridemia	6 (42.9)	8 (57.1)
Hypomagnesemia	7 (63.6)	4 (36.4)

2 patients were not tested for liver alterations. n = sample size.

Hypophosphatemia is the only metabolic alteration that shows a significant association with the length of time on TPN (p=0.005). Other alterations, such as hypernatremia (p=0.058) and hyponatremia (p=0.065), showed p-values close to the significance threshold (Table 4).

Table 4 – Association between metabolic changes and the time of parenteral nutritional therapy in patients at na emergency hospital in Goiânia, GO, Brazil (2024).

Metabolic changes	Time of PNT use (days)		p value*
	Median	IQ	
Liver changes	13	6-18	0.626
Hyperglycemia	10.5	3-14	0.831
Hypoglycemia	13	11- 14	0.238
Hypokalemia	10	3-22	0.122
Hypernatremia	15.5	10-22	0.058
Hyponatremia	3	3-3	0.065
Hypophosphatemia	18	10-22	**0.005**
Hypertriglyceridemia	8	3–15.5	0.744
Hypomagnesemia	14	7–26.5	0.082

PNT = parenteral nutritional therapy; IQ = interquartile range; * = Mann-Whitney U test.

There was no significant association between calorie and protein adequacy and time on parenteral nutritional therapy (PNT) and both patients with longer and shorter time on PNT had calorie and protein inadequacy (Table 5).

Table 5 – Association between the caloric-protein adequacy of parenteral nutritional therapy and the time of use of parenteral nutritional therapy in patients at an emergency hospital in Goiânia, GO, Brazil (2024).

Target	Time of PNT use (days)		p value*
	Median	IQ	
Calories (kcal/kg/day)	13	3-18	0.926
Protein (g/kg/day)	7.5	3-14	0.628

PNT = parenteral nutritional therapy; IQ = interquartile range; * = Mann-Whitney U test.

Table 6 – Association between the caloric-protein adequacy of parenteral nutritional therapy and metabolic alterations in patients at an emergency hospital in Goiânia, GO, Brazil (2024).

Changes	Target							
	Caloric				Protein			
	Achieved (n)	p value*	Not achieved (n)	p value**	Achieved (n)	p value*	Not achieved (n)	p value*
Liver changes	3	0.061	2	0.061	2	0.608	3	0.608
Hyperglycemia	2	0.745	6	0.745	5	0.273	3	0.273
Hypoglycemia	1	0.455	1	0.455	1	0.773	1	0.773
Hypokalemia	1	0.533	6	0.530	3	0.500	4	0.500
Hypernatremia	2	0.500	4	0.500	3	0.716	3	0.716
Hyponatremia	1	0.250	0	0.250	6	0.500	0	0.500
Hypophosphatemia	1	0.778	4	0.778	2	0.500	3	0.500
Hypertriglyceridemia	3	0.159	4	0.159	4	0.500	3	0.500
Hypomagnesemia	1	0.667	3	0.667	1	0.262	3	0.262

* = Fisher test; n = sample size.

There was also no significant association between calorie and protein adequacy and metabolic changes (Table 6).

DISCUSSION

The main result found was the association between time on TPN and hypophosphatemia. However, some results also stood out, such as the association between hepatic alterations and calorie targets reached or not reached and the length of time on TPN and hypomagnesemia, hyper, and hyponatremia.

Veldscholte et al.[19] showed in their study that, for every 1% increase in calorie intake in relation to the percentage of calories expended at rest, there is a 0.002 mmol/l decrease in serum phosphate. Furthermore, patients on PN were more likely to suffer from hypophosphatemia due to the condition associated with refeeding. Lappas et al.[20] stated that the use of parenteral nutrition is a risk factor for refeeding syndrome and electrolyte disorders (hypophosphatemia, hypokalemia and hypomagnesemia).

Electrolyte alterations may be related to refeeding syndrome, since it can manifest in patients with calorie overload in the first 7 days of nutritional therapy and the main marker is hypophosphatemia[8,12]. In the present study, a mean time of 8 days on TPN was correlated with hypophosphatemia ($p<0.005$) and 42.8% (n=6) of the patients studied had calorie overload.

A study carried out in 2020 in a hospital in the Federal District, Brazil, showed that patients who had an increase in TG during the use of parenteral nutrition had greater liver complications, such as an increase in GOT and GPT[21]. A 2017 study also showed a similar result, justifying that this complication could be associated with the patient's clinical condition or the overload of carbohydrates in TPN[22]. In the present study, there was a notable trend between the calorie target offered and liver complications, and hypertriglyceridemia was present in 57% of the patients studied.

Hypo and hypernatremia can be explained by the patients' volume changes during the use of PN and also as an effect of the refeeding syndrome, as it presents common clinical manifestations of water imbalance and hyponatremia[12,21]. Sodium disorders can be the result of excess fluids, nephritis, adrenal insufficiency, ascites, the use of diuretics or excessive fluid losses[23].

The results regarding natremia are inconclusive, as in this study the water balance was not considered in the analysis and the values may be masked by volume replacements made during this period, especially in ICU patients.

Hyperglycemia was the most common alteration found, even when using industrialized formulas that have more stable lipid emulsions, and this can be explained by the calorie overload offered to these patients. This overload may have been due to the fact that these formulas are high in calories and low in protein, requiring a greater volume to adjust the protein supply and consequently offering calories above the patient's needs. One possibility would be to use manipulated formulas according to the patient's needs to avoid this overload, but these formulas are not standardized in the hospital.

Another possibility for electrolyte alterations is insufficient replacement of trace elements during the use of PNT. One study analyzed the percentage of adequacy of these

replacements and found that sodium, potassium, phosphorus, magnesium and calcium had replacements below the daily needs of the patients[24]. This statement demonstrates the need for careful monitoring of these patients and efficient action by the multiprofessional nutritional therapy team (MNTT). The trace element emulsion available at the hospital only contains zinc, copper, manganese and chromium. In this way, patients only receive the electrolytes present in standardized NPT formulations and replacements are made only after their serum drops.

This study had some limitations. There was as a small patient population, lack of adherence by the medical team to the requests for laboratory tests in accordance with the hospital protocol for parenteral nutritional therapy, and few patients using exclusive NPT, as most of the patients during this period were on mixed feeding. There also was a failure to monitor patients with previous hypertriglyceridemia.

For future studies, it would be necessary to train the hospital protocol before starting data collection, as well as to consider a longer collection time and to also monitor patients with previous hypertriglyceridemia. The reference value to be considered for hypertriglyceridemia during the use of TPN should be changed (≥400 mg/dL), according to Hartl et al.[25]. Patients on mixed feeding should also be investigated, with the possibility of comparing groups. Worthington et al.[26] strengthen this idea, affirming the need to periodically monitor glucose levels, liver function, electrolytes and triglycerides in hospitalized patients using TNP. According to Granjeiro et al.[21], there is weakness in the hospital care team's monitoring of this public.

CONCLUSION

It is possible to conclude that patients who receive calorie overload at the start of TPN may present important markers for feedback syndrome such as hypophosphatemia, hypokalemia and hypomagnesemia, as well as hypertriglyceridemia, hypernatremia, hyperglycemia and liver alterations.

Establishing a well-structured and trained MNTT to accompany these patients is an important barrier to such complications.

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Study location: Hospital de Urgências de Goiás, Goiânia, GO, Brasil.

Conflict of interest: The authors declare there are none.