

Transient Hyperglycemia During Childhood Acute Lymphocytic Leukemia Chemotherapy: An Old Event Revisited

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Keywords

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Abstract: Hyperglycemia has been described as a common event occurring during acute lymphocytic leukemia chemotherapy. It is associated with the synergistic effect of L-asparaginase and glucocorticoids, and related to poor outcome. Our goal was to compare clinical and laboratory findings between hyperglycemic episodes occurring during childhood acute lymphocytic leukemia induction chemotherapy. Here we describe 12 (3.8%) high-risk patients of 311 total patients, 9 (75%) of who are female. The 12 patients presented with 16 hyperglycemic episodes classified into adverse or satisfactory categories. There were no differences in clinical or laboratory variables among groups, although the majority of episodes occurred in pubescents, regardless of the type of glucocorticoid employed. Despite the fact that only 1 patient was overweight, pancreatitis was not diagnosed. Although we could not determine whether hyperglycemia predicts an adverse outcome, glucose evaluation played an important role during induction chemotherapy. To date, recognized risk factors for hyperglycemia no longer explain our findings, thus other mechanisms related to insulin secretion and action should be further studied.

Introduction

The tremendous improvement in survival of children diagnosed with cancer has resulted in a growing population that experiences at least one late effect. Long-term complications in childhood cancer survivors, such as growth impairment or endocrine dysfunction, are well known and not only related to the specific therapy used—chemotherapy and radiotherapy—but also determined by individual host characteristics.¹

Nonetheless, short-term adverse effects of cancer treatment protocols should call our attention to their potential influence on morbidity. Hyperglycemic hyperosmolar nonketotic syndrome and diabetic ketoacidosis—life-threatening acute complications—have

been rarely reported as adverse effects in children during acute lymphocytic leukemia (ALL) induction chemotherapy.²⁻⁵ In contrast, transient hyperglycemia (TH) has been described as a common event during ALL induction chemotherapy in both adults and children and still remains a complication that is not well understood.⁶⁻⁸ Thus far, TH has been considered an adverse effect of an L-asparaginase and glucocorticoid (either prednisone or dexamethasone) synergistic effect, possibly interfering with insulin production, release, and action.^{3-5,9-15} Nevertheless, it must be considered that leukemia alters glucose metabolism, and hyperglycemia may have an influence upon leukemic cell proliferation.¹⁶ In addition, patients who develop TH during induction chemotherapy may face increased risk for complicated infections, increased mortality, and disease recurrence.^{5,6,8,17} Therefore, various predisposing risk factors for TH must be recognized.¹⁸

Our goal was to evaluate clinical and laboratory findings in patients that developed TH during ALL induction chemotherapy and to compare hyperglycemic episodes with respect to clinical outcome.

Material and Methods

Study Population

We retrospectively collected medical records of all hyperglycemic episodes occurring in ALL pediatric patients below the age of 18 years during the induction phase of chemotherapy at the Pediatric Oncology Institute-IOP/GRAACC, at the Federal University of Sao Paulo-UNIFESP/EPM in Brazil from April 1994 to November 2006.

Patients were treated with chemotherapy regimens based on the Brazilian Group for Treatment of Leukemia in Childhood (GBTLI)¹⁹ protocol or with alternative protocols when relapse occurred, with similar glucocorticoid and L-asparaginase doses. The GBTLI induction chemotherapy phase consisted of standard drug administration lasting 28 days, comprising vincristine 1.5 mg/m², daunorubicin 25 mg/m², *Escherichia coli* (*E. coli*) derived L-asparaginase (5,000 IU/m² × 9), and glucocorticoid therapy (oral daily for 4 weeks) consisting of either dexamethasone (6–8 mg/m²), prednisone (40 mg/m²), or prednisolone (60 mg/m²) in corresponding doses. Patients were considered to be at high risk for disease recurrence if they were diagnosed before 1 year of age or at older than 9 years, had a white blood cell count at or above 50,000/mm³, and had poor response to therapy and/or occurrence of blast cells in the central nervous system on day 14.¹⁹

Hematologic relapse of ALL, occurring at any time during therapy or after completion of treatment, was defined as the presence of 5% or more of abnormal blast cells in bone marrow tests. Hematologic remission was

defined as the absence of disease in marrow or blood, characterized by less than 5% of blast cells and reinduction chemotherapy as another phase of induction chemotherapy following relapse.

Methods

Clinical Data Clinical data that was analyzed included gender, age at ALL diagnosis, family history of diabetes mellitus, number of hyperglycemic episodes, age during episode, pubertal stage at diagnosis and episode, glucocorticoid type and dose employed, drug and number of doses related to TH (steroid or L-asparaginase), body mass index (BMI) and respective z-score, follow-up, and clinical outcome. Hyperglycemic events were classified into adverse outcome (comprising patients with relapse of the disease and/or death any time during therapy or after therapy withdrawal) and satisfactory outcome (including those patients who achieved complete remission at any time during therapy or anytime off therapy).

Pubertal development was evaluated according to Marshall and Tanner staging, with stage 1 defined as prepubertal and stages 2–5 defined as pubertal.^{20,21} BMI was calculated as weight in kilograms divided by height in meters squared. Age and gender-standardized BMI z-scores were calculated using height, weight, gender, and age data based on the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS) 2000 growth curves.²² Children and adolescents were defined as overweight if they had a BMI greater than 2.0 standard deviation scores (SDS).^{23,24}

Laboratory Data Laboratory data collected for analysis included glucose and amylase peak for all hyperglycemic episodes and C-peptide and glycated hemoglobin (HbA1C) for some selected events. During induction chemotherapy, blood glucose and amylase levels were checked at least twice a week before and after L-asparaginase administration, and more often if glucose was consistently elevated. Glucose and amylase peaks were considered for comparisons. Hyperglycemia was defined as 2 or more random glucose determinations at or above 200 mg/dL during the first 28 days of induction chemotherapy according to the guidelines of the American Diabetes Association (ADA).^{7,8,25} Glucose was evaluated by a colorimetric enzymatic method. Pancreatitis was defined as amylase 3 times above the upper limit of normal (110 IU/L), assessed by a monoclonal antibody inhibition assay.

C-peptide (immunofluorometric assay) and HbA1C (high performance liquid chromatography) were used for further assessment in some selected episodes; however, there was no defined outline for this assessment. Normal ranges for C-peptide and HbA1C were 0.36–3.59 ng/mL and 4.0–6.0%, respectively.

Table 1. Comparison of Pubertal Stage at Diagnosis/Episode, Glucocorticoid Type, and Therapy Phase Related to Hyperglycemia with Respect to Clinical Outcome in 16 Hyperglycemic Episodes

	Clinical Outcome			Fisher's Exact Test (<i>P</i>)
	Adverse (n=9)	Satisfactory (n=7)	Total (n=16)	
Pubertal stage at diagnosis/episode				<i>P</i> =.585
Prepubescent/prepubescent	1 (11.1%)	2 (28.6%)	3 (18.7%)	
Prepubescent/pubescent	2 (22.2%)	0 (0%)	2 (12.5%)	
Pubescent/pubescent	6 (66.7%)	5 (71.4%)	11 (68.8%)	
Glucocorticoid type				<i>P</i> =1.00
Prednisone or (methyl)prednisolone*	5 (55.6%)	4 (57.1%)	9 (56.2%)	
Dexamethasone	4 (44.4%)	3 (42.9%)	7 (43.8%)	
Therapy phase with respect to hyperglycemia				<i>P</i> =.310
Before therapy	1 (11.1%)	0 (0%)	1 (6.2%)	
Steroids only	2 (22.3%)	2 (28.6%)	4 (25%)	
L-asp 1st–3rd dose	3 (33.3%)	5 (71.4%)	8 (50%)	
L-asp 4th–6th dose	3 (33.3%)	0 (0%)	3 (18.8%)	

L-asp=L-asparaginase.

Pubescents=Patients with stages 2–5 according to Marshall and Tanner pubertal staging^{20,21}; Prepubescents=Patients with stage 1, according to Marshall and Tanner pubertal staging.^{20,21}

*The patient who developed hyperglycemia prior to steroid therapy was considered in this analysis, as she underwent methylprednisolone pulse therapy.

Statistics Since the sample size was too small for statistical inferences, a descriptive analysis of hyperglycemic episodes was performed. Comparisons between adverse and satisfactory events with respect to clinical and laboratory variables were performed using Fisher's exact test and independent samples *t* tests. All statistical tests were conducted at the 0.05 level of significance.

Results

Study Population

The study population was made up of 12 (3.8%) high-risk ALL patients under the age of 18, with no previous diagnosis of diabetes, presenting with TH. Nine of the patients (75%) were female, and 3 (25%) had a positive family history of diabetes mellitus. ALL in hyperglycemic patients was diagnosed at a mean age of 11.5 ± 3.9 years, and patients were treated according to the GBTLI and/or alternative regimens with standard glucocorticoid and L-asparaginase doses. All patients fully completed the first 28 days of induction chemotherapy.¹⁹

Clinical Data

There were 16 hyperglycemic episodes observed, occurring at a mean age of 12.3 ± 3.8 years, which were classified according to clinical outcome: 9 of 16 (56.3%) episodes were considered adverse and 7 of 16 (43.7%) satisfactory. Four of 12 (33.3%) patients had 2 episodes each, and according to clinical outcome, 2 of 4 patients presented with adverse/satisfactory episodes (1 female and 1 male, relapsed after their first episode of TH, but reached clinical remission after a second episode of TH) and 2 of 4 patients with adverse episodes (2 females, encompassing relapses and death). Insulin therapy was needed in all hyperglycemic events, and due to glucose alterations, L-asparaginase administration was occasionally delayed because patients had to reestablish glucose control.

There were no differences in hyperglycemic episodes in regard to clinical outcome (*P*=1.00) according to gender. Additionally, the majority of episodes occurred in patients who were already pubescents at diagnosis (11/16; 68.8%); however, no differences in pubertal stage were recorded among patients with adverse and satisfactory episodes (*P*=.585; Table 1). Moreover, there were no differences

Table 2. Comparison of Clinical and Laboratory Variables With Respect to Clinical Outcome in 16 Hyperglycemic Episodes

		Hyperglycemic Episodes		Total (n=16)	T-test (P)
		Adverse (n=9)	Satisfactory (n=7)		
Age at hyperglycemic episodes (yr)	Mean ± SD	12.7 ± 3.9	11.8 ± 3.8	12.3 ± 3.8	.667
	Min–Max	3.5–17.0	5.5–15.4	3.5–17.0	
BMI (kg/m ²)	Mean ± SD	19.5 ± 6.1	19.0 ± 2.8	19.2 ± 4.8	.859
	Min–Max	14.8–34.9	14.5–22.5	14.5–34.9	
BMI SDS	Mean ± SD	-0.28 ± 1.20	0.25 ± 0.58	-0.04 ± 0.99	.292
	Min–Max	-1.40–2.57	-0.76–1.02	-1.40–2.57	
Glucose peak (mg/dL)	Mean ± SD	549.9 ± 278.1	476.3 ± 165.2	517.7 ± 231.5	.547
	Min–Max	225–1,075	300–776	225–1,075	
Amylase peak (IU/L)	Mean ± SD	81.8 ± 51.6	61.0 ± 32.3	72.7 ± 44.2	.366
	Min–Max	23–171	17–114	17–171	

BMI=body mass index; BMI SDS=BMI standard deviation scores.

between adverse and satisfactory outcome groups when comparing chronologic age at the time of hyperglycemic events (12.7 ± 3.9 vs 11.8 ± 3.8 years; $P=.667$), as well as no differences between BMI and BMI SDS (19.5 ± 6.1 kg/m² vs 19.0 ± 2.8 kg/m²; $P=.859$ and -0.28 ± 1.20 vs 0.25 ± 0.58 SDS; $P=.292$, respectively). However, BMI SDS showed a large variability, so that the group with an adverse outcome tended to present a decreased BMI SDS. Only 1 patient, who presented with a single adverse episode, was considered overweight at the time TH was diagnosed. Nonetheless, even after excluding this patient from BMI analysis, no significant differences were obtained. In addition, statistical data were similar for all variables when a nonparametric test (Mann-Whitney test) was performed, except for BMI SDS, which confirmed a tendency to be decreased in the group with an adverse outcome ($P=.071$; Table 2 and Figure 1).

Regarding glucocorticoid type and dose employed during induction chemotherapy, all hyperglycemic events occurred while patients were on steroid therapy, except in 1 of 16 episodes (6.2%). This specific patient presented TH at ALL diagnosis before steroid therapy was introduced, although during follow-up, she underwent a methylprednisolone pulse therapy. The remaining 15 episodes (93.8%) occurred throughout glucocorticoid therapy: 7 of 16 (43.8%) occurred during prednisone administration (40 mg/m²), 7 of 16 (43.8%) occurred throughout dexamethasone therapy (6–8 mg/m²), and only 1 episode (6.2%) was reported during prednisolone administration (60 mg/m²). When

comparing clinical outcome, there were no differences in glucocorticoid type employed ($P=1.00$). The patient who presented with hyperglycemia before steroid therapy was included in this analysis, as she was afterward treated with methylprednisolone (Table 1).

In the chemotherapy phase, the hyperglycemic episodes revealed the following distribution: 1 of 16 (6.2%) occurred before therapy was started, 4 of 16 (25%) during steroid administration only, and the remaining 11 of 16 episodes (68.8%) occurred unpredictably at any L-asparaginase dose, but predominantly during initial doses. None of the episodes had occurred at or above the seventh dose of L-asparaginase. No differences were recorded between adverse and satisfactory episodes ($P=.310$; Table 1).

In addition, when clinical data of hyperglycemic events were compared—taking into account those that occurred before therapy, during steroid administration only, and after any dose of L-asparaginase—no differences were recorded, even though the analysis was entirely descriptive.

Laboratory Data

There were no differences in glucose peak between adverse and satisfactory episodes (549.9 ± 278.1 mg/dL vs 476.3 ± 165.2 mg/dL; $P=.547$). However, glucose levels tended to be higher in the adverse group and showed a large variability, although no significant differences were encountered. No patient was diagnosed as having pancreatitis according to clinical signs and amylase levels, and amylase concentrations were not different between

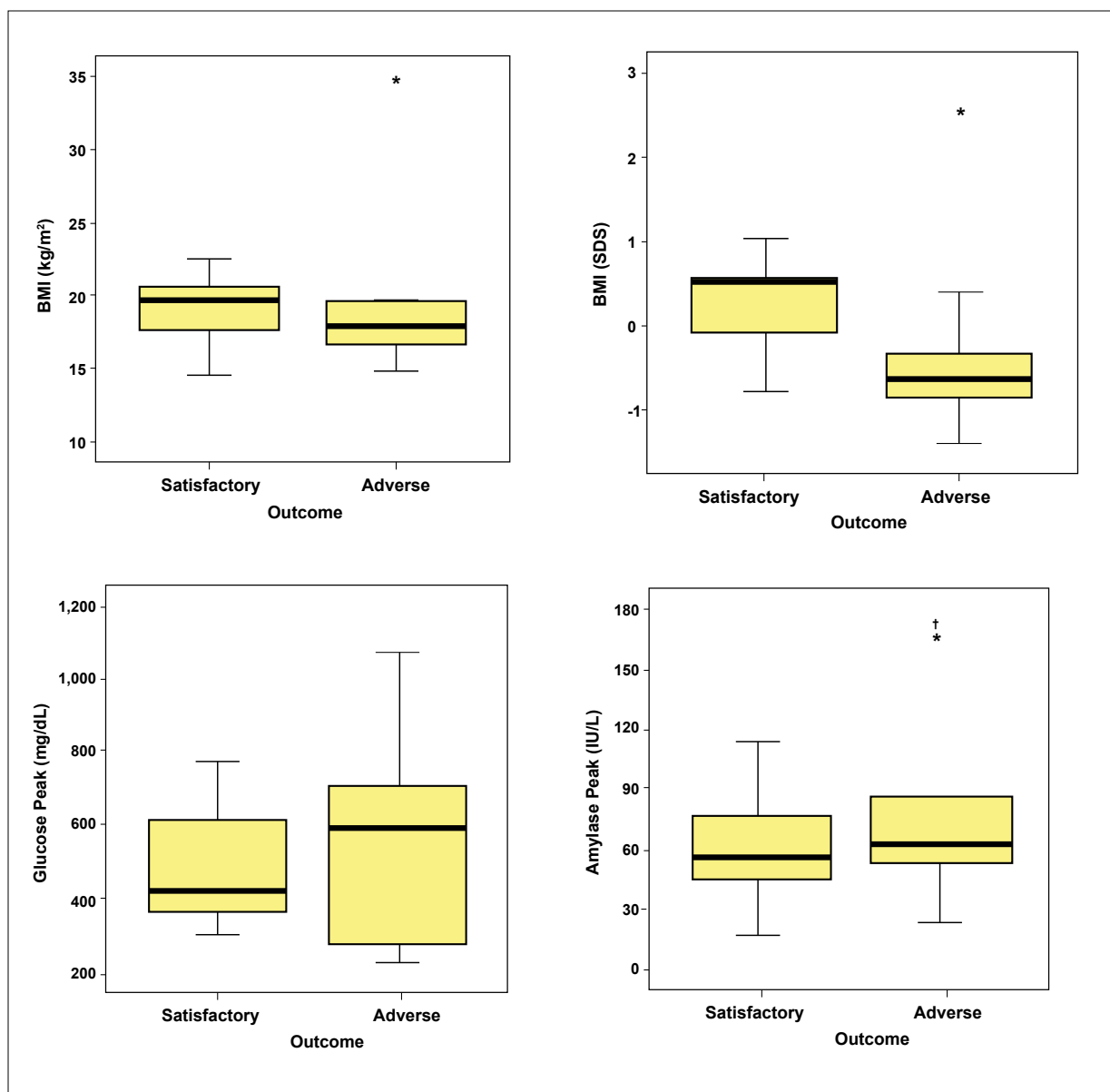


Figure 1. Boxplot of body mass index (BMI), BMI standard deviation scores (SDS), glucose, and amylase peak levels with respect to clinical outcome in 16 hyperglycemic episodes.

*One patient had a BMI of 34.9 kg/m², a BMI SDS of 2.57, and an amylase peak of 164 IU/L

†One patient had an amylase peak of 171 IU/L

groups (81.8 ± 51.6 IU/L vs 61.0 ± 32.3 IU/L; $P=.366$). Statistical data were similar when the Mann-Whitney test was performed (Table 2 and Figure 1).

When laboratory data of hyperglycemic events were compared, once again taking into account those events that occurred before therapy, during steroid administration only, and after any dose of L-asparaginase, no differences were observed.

C-peptide assessment in 6 of 16 (37.5%) episodes showed levels within the normal range, but it was near 2

times higher than the upper limit of normal in 2 patients. HbA1C evaluation in 6 of 16 episodes (37.5%) was 2.3% and 0.8% above the upper limit of normal, respectively, in 2 patients (in one patient at second relapse). There were no differences recorded between clinical outcome groups.

Discussion

Glucose metabolism alterations have always been a matter of debate in patients with cancer. The association between

diabetes mellitus and cancer was reported more than 100 years ago, recognizing the disease as a risk factor for the development of breast, endometrial, colorectal, and pancreatic carcinomas.²⁶ Currently, hyperinsulinemia and its resulting metabolic abnormalities, as well as impaired pancreatic β -cell function including diabetes mellitus itself, have been reported in long-term survivors of ALL.²⁷⁻³¹ Nonetheless, hyperglycemia has also been described as an acute adverse event that occurs during chemotherapy for ALL in adults and children. To date, various emerging studies have assessed the incidence of TH in this particular group of patients and its relationship with chemotherapy.^{6-8,17,18} Since already reported in ALL patients, 37% of adults⁷ and 4–20% of children^{6,8,17,18} may experience TH during induction chemotherapy, particularly those with any of the following risk factors: age above 10 years, female gender, obesity at the initiation of chemotherapy, family history of diabetes mellitus, dexamethasone administration, use of native L-asparaginase, and Down syndrome. Our study population comprised only 12 ALL patients who presented with TH during induction chemotherapy, which is less than that observed in previous reports, even though the range of occurrence is rather wide.^{6-8,18} However, there were several limitations in the present study. First, the prevalence of glucose impairment: since there was no standard for routine glucose control, patients without significantly elevated glucose levels, asymptomatic hyperglycemia, or mild transient glucose alterations with no insulin requirement may have remained undiagnosed.

The use of hyperglycemic events rather than individual patients as the denominator for statistical analysis is another limitation of this study. Patient outcome (relapse or death) subsequent to the hyperglycemic events, as well as the mixing of data from those patients that went through 2 episodes of TH, is also of concern, as many factors rather than just hyperglycemia may have influenced disease relapse. For this retrospective and descriptive analysis of the hyperglycemic episodes during ALL induction chemotherapy, all transient episodes were included, even those that occurred at relapses. The purpose of this study was to evaluate and to compare clinical and laboratory data of patients with hyperglycemic episodes, and the 4 patients with 2 episodes each were certainly counted twice in the analysis, but at completely different time points, meaning different age, BMI, glucose and amylase peak levels, and a different therapeutic phase of treatment.

As stated previously, females were affected more than males, but no differences in respect to the outcome were recorded among genders in our study.⁸ However, our findings contrast with a recent statement according to which, female gender can no longer be considered a risk factor for the development of TH during induction chemotherapy.¹⁸ Age at hyperglycemic episode was also an important factor in our study, given that it has been

considered a risk factor for TH¹⁸ and because it is one of the criteria used in GBTLI to classify patients according to the risk for disease recurrence.¹⁹ All patients included in the study group were considered high risk for recurrence, and all with the exception of 2 were older than 10 years of age during TH episodes. Compared to the whole population of ALL patients diagnosed in our institution (IOP/GRAACC) during the study period, the TH group certainly was considered older at diagnosis (mean age, 11.5 ± 3.9 years), as ALL is frequently diagnosed in preschool children aged 3–5 years. However, those 12 patients with TH were comparable to the cohort of high-risk ALL patients in terms of age at ALL diagnosis.¹⁹

Baillargeon and coauthors showed that chemotherapy-induced hyperglycemia depends on genetic predisposition that could be triggered not only by obesity, but also by ethnic factors and puberty.⁸ Lowas and colleagues have also pointed out that obesity during induction chemotherapy is an important predictor of TH.¹⁸ Contrary to previous reports, in our study population, neither obesity nor a family history of diabetes mellitus was positively associated with hyperglycemia.^{6-8,18} Obesity did not play a major role in the development of hyperglycemia and there were no significant differences in BMI among clinical outcome groups. Although, in contrast with preceding data,^{8,18} those patients with an adverse outcome showed a tendency for a decreased BMI even though BMI SDS presented with a large variability. So far, only 1 patient showed BMI over 2.0 SDS while he developed hyperglycemia, and only 3 of 12 patients (25%) had a family history of diabetes mellitus. In addition, the majority of patients were pubescent at ALL diagnosis, and likewise at hyperglycemic episode. They were therefore classified as high risk for disease recurrence, and were possibly susceptible to metabolic changes that worsened throughout puberty, which concurs with the findings from Baillargeon and coauthors.⁸ Along with age, puberty may also have been considered a risk factor for TH.

Hyperglycemia is an event that has yet to be fully understood, but so far it has been considered an adverse effect of an L-asparaginase and glucocorticoid (either prednisone or dexamethasone) synergistic effect.^{3-5,9-15,17,18} L-asparaginase, an enzyme with established antileukemic activity, exerts a direct toxic effect on the pancreatic β -cell via inhibition of insulin production and release, impairing insulin receptor function, or indirectly via induction of pancreatitis resulting in hyperglycemia.^{5,11,12-14} Native L-asparaginase was considered a predictor of hyperglycemia according to a recent statement by Lowas and colleagues.¹⁸ Nonetheless, the number of patients affected to a clinically relevant degree is small and has decreased with the use of the better purified preparations currently available (*Erwinia carotovora* derived).³²⁻³⁵

According to previous data, the incidence of L-asparaginase-associated pancreatitis in children is 2–16%.^{13,14,36,37} However, none of our patients who developed TH, all treated with derived L-asparaginase, presented with pancreatitis. Therefore, L-asparaginase-associated pancreatitis no longer explains the development of TH in our study population, and other mechanisms of insulin secretion and action must be considered.

Corticosteroids strongly interfere with glucose metabolism, decreasing glucose utilization by muscle and adipose tissue and decreasing the responsiveness of these tissues to insulin, thus predisposing patients to insulin resistance.^{5,15} Previous statements hypothesized that patients receiving dexamethasone would be more likely to experience TH, and the addition of daunorubicin led to a much larger increase in dexamethasone-related toxicity compared to prednisone, even though it has been a controversial issue.^{15,18} Thus far, daunorubicin was given to all patients, as they were all considered high risk for recurrence of ALL; however, no differences in the rates of hyperglycemia were recorded among clinical outcome groups with regard to glucocorticoid type and dose used. In addition, when clinical and laboratory data of patients that developed TH before therapy, during steroid administration only, and after any dose of L-asparaginase were compared, no differences were recorded.

To date, patients in our study who are still alive have not presented with glucose alterations. However, we cannot predict if their endocrine pancreatic function, that is apparently recovered, will function properly. The majority of ALL patients who developed therapy-induced TH recovered when L-asparaginase and glucocorticoid were discontinued.³⁸ A recent study has stated that chemotherapy is associated with pancreatic β -cell function damage, which persists after therapy withdrawal.²⁸ In general, it is quite clear that β -cell function might be impaired in some patients treated for ALL, but the exact mechanism responsible for the alterations is not completely understood yet.

Thus far, inhibition of insulin synthesis or insulin receptor synthesis may play a role in insulin deficiency or resistance in ALL patients presenting with TH.^{11,12} C-peptide values in some selected events were normal or above the upper limit of normal, reflecting a normal insulin production, but it is not possible to conclude whether these patients were insulin resistant or not. Until now, there has been a lack of information on the possible role of insulin receptors in leukemic patients. Carpentieri and coworkers confirmed reduced insulin binding after L-asparaginase administration, possibly attributed to mechanisms such as aggregation or inaccessibility of receptor structures, with modification in conformation. A reduced synthesis of new receptors secondary to hypo-

insulinemia is also a possibility, as the production of insulin receptors is regulated by the levels of the hormone itself. The results were obtained from a study performed only on 4 patients, and further data are still required.¹¹ Moreover, it is possible that leukemia may alter glucose metabolism, and hyperglycemia may have an influence on leukemic cell proliferation.¹⁶ In our study, there was a pubescent female patient who developed hyperglycemia before therapy was started, and died afterward. Overall, treatment-related hyperglycemia may not be caused exclusively by drugs (L-asparaginase or steroids), and other metabolic derangements, not entirely understood, might be involved in the process.

The main concern with ALL children who develop TH at diagnosis or any time during treatment is whether this metabolic disorder may have any correlation with disease outcome. Data from an M.D. Anderson Cancer Center study performed in adult patients showed short complete remission duration in those patients that presented hyperglycemia during induction chemotherapy. Those patients were also more likely to develop sepsis and any complicated infection, compared with patients without hyperglycemia. A recently published statement regarding childhood hyperglycemia concurs with the prior statement that overt hyperglycemia is an important risk factor for infection complications in children with ALL during the first year of treatment.¹⁷ The connection between poor outcome and impaired glucose tolerance is multifactorial, including altered metabolism that supports the proliferative state of leukemic cells and impaired immune function. Alterations in cytokine production due to immune dysregulation may lead to the risk of TH in ALL patients, similar to that observed in septic patients.^{5,7} The relapse rate is approximately 20% in IOP/GRAACC–UNIFESP/EPM, Sao Paulo, Brazil (unpublished data). However, according to the current data, we cannot determine whether recurrence or adverse outcome was more prevalent among hyperglycemic patients, as only patients whose glucose levels were at or above 200 mg/dL—all requiring insulin therapy—were included. Nonetheless, we have no clinical, laboratory, or outcome data from those patients who did not develop hyperglycemia in order to make comparisons and determine whether or not hyperglycemia predicts poor outcome. However, clinical and laboratory data were not influenced by clinical outcome in our statement.

Conclusions

In conclusion, glucose evaluation plays an important role during induction chemotherapy, particularly in females throughout puberty. Therefore, they are considered at high risk for recurrence. In our data, the recognized risk factors for TH including obesity, family history of diabetes

mellitus, L-asparaginase-induced pancreatitis, and type of glucocorticoid employed, no longer explain our findings, and to date, the synergistic effect of both L-asparaginase and glucocorticoids leading to other mechanisms that are still not well understood must be considered. Although we cannot evaluate whether hyperglycemia might be a predictor of an adverse outcome, we can conclude that ALL patients must have close follow-up, and all glucose alterations, including the subtle ones, must be considered and promptly treated in order to prevent worsening of clinical conditions. An ideal study would include prospective measurements of glucose in all patients during ALL induction chemotherapy to determine any clinical and laboratory differences, as well as clinical outcome (including relapses, infections and/or death) between those with and without hyperglycemia in order to establish risk factors. To date, leucocytes and insulin receptors should be further studied to better understand the unknown mechanisms involved in this type of transient diabetes.

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