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ORIGINAL ARTICLE

# Medication induced diabetes during induction in pediatric acute lymphoblastic leukemia: prevalence, risk factors and characteristics

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**Abstract**
*Introduction* Medication induced diabetes (MID) during induction therapy (MIDi) in patients with acute lymphoblastic leukemia (ALL) is not well characterized in children, with recent studies yielding conflicting results.
*Purpose* The purpose of the study was to describe the prevalence of MIDi and risk factors for its development.
*Methods* We retrospectively gathered demographic, disease course and treatment data on 363 patients aged 1 to 17.9 years diagnosed with ALL at a pediatric tertiary care hospital between 1998 and 2005. MIDi was defined as blood glucose ≥200 mg/dL (11.1 mmol/L) on at least 2 separate days during induction.
*Results* Fifty-seven subjects (15.7%) developed MIDi during the study period. Patients ≥10 years were more likely to develop MIDi than those <10 years (odds ratio [OR] 9.6, 95% confidence interval [CI] 5.1–17.8). BMI percentile among those with MIDi (mean±SD 58.2±31.0) did not differ from those without MIDi (52.2±32.0, $P$=0.429). The presence of Trisomy 21 (OR 3.6, 95% CI 1.1–11.4, $P$=0.030) and CNS involvement at diagnosis (OR 3.8, 95% CI 1.4–10.1, $P$=0.009) were associated with an increased risk of MIDi. After adjustment for potential confounding variables, age ≥10 years and the presence of CNS disease at diagnosis remained significantly associated with MIDi.
*Conclusions* Older age and CNS involvement at diagnosis increase the risk of MIDi. In contrast to previous studies, higher BMI was not associated with MIDi in our population.

**Keywords** Hypergylcemia · ALL · Induction · Pediatric · Glucocorticoids · Asparaginase

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## Introduction

Hyperglycemia is a well-recognized complication of several chronic diseases [1, 2]. In childhood, hyperglycemia and secondary diabetes (persistent and/or symptomatic hyperglycemia) is seen most commonly during treatment of malignancies such as acute lymphoblastic leukemia (ALL), after organ and bone marrow transplantation, and as part of infiltrative or destructive conditions of the pancreas, such as cystic fibrosis [3–6].

In ALL, potential factors triggering hyperglycemia include direct infiltration of the pancreas by leukemic cells, beta cell dysfunction induced by chemotherapeutic agents such as L-asparaginase, and increased insulin resistance and hepatic gluconeogenesis secondary to glucocorticoids [4]. Most patients have a transient form of hyperglycemia—medication induced diabetes (MID)—which appears to resolve after discontinuation or tapering down of the glucocorticoid therapy.

The epidemiology of MID has been well documented in adults [7–9], but has been less well studied in the pediatric population. Although studies of pediatric patients with ALL have provided useful information, many of them are small and focus on select populations. In addition, the more recent studies of hyperglycemia during induction have conflicting results, which make it difficult to identify those at greatest risk of developing MID [10–13].

MID is commonly observed in ALL during induction chemotherapy. Thus, we focused on this phase of therapy. The aim of our study was to determine the prevalence of MID during induction therapy (MIDi) for ALL, as well as to explore patient and treatment related risk factors for the development of diabetes in our cohort.

## Methods

### Study population

The study cohort consisted of all consecutive patients aged 1 to 17.9 years, diagnosed with B precursor-cell or T-cell ALL, at The Hospital for Sick Children, Toronto, Canada, between January 1, 1998 and December 31, 2005. Our hospital is a large tertiary care hospital servicing a diverse population of children from Toronto and the surrounding areas.

The following protocols were used during the study period for patients with B lineage ALL: from 1998 to 1999, either POG 9605, or our institutional three-drug (protocol AB) or four-drug (protocol C) regimen; from 2000 to 2004, the POG 9900 series which includes a three-drug and a four-drug induction; and from 2004 onward, COG AALL0331 or AALL0232. Patients with T-cell ALL from 1997 to 1999 received protocol C and COG A5971 after 1999. The three-drug induction regimen consisted of vincristine, L-asparaginase and either prednisone or dexamethasone; the four-drug regimen consisted of vincristine, L-asparaginase, daunomycin and either prednisone or dexamethasone. Prednisone dose was 40 mg/m$^2$/day in most protocols, and that of dexamethasone was 6 mg/m$^2$/day. The prednisone and dexamethasone doses have similar glucocorticoid effect and should therefore be associated with similar risks for the development of MIDi [14]. L-asparaginase was given as six doses of 10,000 units/m$^2$/day or nine doses of 6000 units/m$^2$/day over the first 21 days of induction to all subjects. At admission, patients received hydration at 3 L/m$^2$ and allopurinol with or without alkalinization for tumor lysis precautions. Some patients may have received rasburicase. In most cases normal saline was used for hydration.

We excluded patients who were less than 1 year of age at diagnosis, due to the well documented difference in manifestations, outcome and treatment modalities used in this age group [15]. We also excluded patients with previously recognized diabetes, as well as patients who were treated with glucocorticoids for other indications.

### Data collected

We reviewed the charts of all study subjects and extracted information pertaining to (a) demographic parameters including age at diagnosis, gender, height, weight, white blood cell count (WBC) at presentation and diagnosis of Down syndrome, (b) disease course such as central nervous system involvement, and death, and (c) treatment variables including type of glucocorticoid used, dose and anthracycline use.

Hyperglycemia in this population has been defined in a number of different ways in the literature [10–13, 16]. In order to isolate a group with more persistent hyperglycemia, only patients with a plasma glucose level greater than or equal to 11.1 mmol/L on 2 separate days or more were considered to have MID. The primary outcome of interest was MID during induction (MIDi). The definition is in accordance with the American Diabetes Association definition [17]. This definition is also consistent with previous studies of drug induced diabetes in this population [10–12]. All patients had blood glucose level measurements as part of routine blood work drawn daily for the duration of their hospital admission for induction but did not routinely have pre-treatment glucose levels measured. During this time period, children with newly diagnosed ALL were hospitalized for at least 8 to 14 days of induction chemotherapy. Patients who demonstrated persistently elevated blood glucose levels (over 2 days or more) or glycosuria were monitored more closely.

We calculated body mass index (BMI) as weight in kilograms divided by height in square meters and converted these values into age-specific and gender-specific Z-scores and percentiles using the Center for Disease Control (CDC) growth curves [18]. Because of the CDC recommendation to use BMI values only after the age of 2 years, subjects under the age of 2 were not included in the BMI analysis.

### Statistical analysis

We studied the association between patient, disease and treatment related variables and the development of MIDi using univariate logistic regression. We performed a multivariate logistic regression analysis to adjust for potential confounding variables. Any independent variables found to be associated with the outcome at the $P<0.1$ level or below were considered for inclusion in the multivariate regression model as well as any variables felt to be clinically relevant. We analyzed BMI as both a continuous and categorical variable using CDC definitions of values of 85th percentile for overweight and 95th percentile for obese [14]. An age cutoff of 10 years was selected for categorical comparisons based on findings in previous studies [11, 16]. WBC count was analyzed both as a continuous and categorical variable using a total WBC count of $50\times10^9$/L as the acceptable cutoff for high versus standard risk leukemia [19].

## Results

### Study subjects

Within the study period, 364 patients aged 1 to 17.9 years were diagnosed with ALL. One patient was excluded from the study because of pre-existing type 1 diabetes mellitus. Average follow-up period was 5.9 years (range 2.0–10.0 years). Of the 363 subjects included, 222 (61.2%) were male. Mean age at diagnosis (±SD) was 6.4 (±4.2) years (range 1–17.9 years). Mean BMI percentile (±SD) was 53.2 (±31.8). Fifty-seven (15.7%) patients developed MIDi. In the study sample 13 patients (3.6%) had Trisomy 21, and 18 patients (5%) presented with central nervous system disease at the time of diagnosis. At the time of study there had been 30 deaths (8.3%) in the study sample (Table 1).

### Associations with MIDi

Associations with MIDi using univariate logistic regression can be seen in Table 1. Subjects who developed MIDi were significantly older at diagnosis than subjects who did not develop MIDi. Patients ≥10 years were more likely to develop MIDi than those younger than 10 years with an OR of 9.6 (95% CI 5.1–17.8, $P<0.001$). Mean BMI in the MIDi group was higher than in the group without MID. This difference was not sustained when the BMI percentiles were calculated thereby adjusting for age and gender. There was no association between BMI≥85th percentile (overweight) or BMI>95th percentile (obese) and the presence of MIDi (Table 1). The presence of Trisomy 21 was associated with an increased likelihood of MIDi with an OR of 3.6 (95% CI 1.1–11.4, $P=0.030$). WBC at presentation was not associated with increased risk for MIDi when assessed as a continuous variable ($46.1\pm78.9\times10^9$ WBC/L in the MID group vs. $36.6\pm77.9\times10^9$ WBC/L in the non-MDI group, $P=0.43$). When using a cutoff value of $50\times10^9$ WBC /L, a higher WBC count was not associated with increased risk for MID either ($P=0.24$, Table 1).

All patients received either prednisone or dexamethasone as part of their induction treatment. There was no association between the type of glucocorticoid used and the development of MIDi. Of prednisone treated patients 16.2% developed MIDi vs. 14.3% of dexamethasone treated patients ($P=0.683$). Presence of central nervous system disease at diagnosis was associated with an increased risk of MIDi with an OR of 3.8 (95% CI 1.4–10.1, $P=0.009$).

During the follow-up period, there were 30 cases of death. MIDi was more prevalent in those who died with 10 (33.3%) cases of MIDi occurring among those who died with the remaining 47 (14.1%) cases of MIDi occurring among those who were alive at the time of the study (OR= 3.0 (95% CI 1.3–6.9, $P=0.008$)).

Of the MIDi group 31 (54%) had additional episodes of hyperglycemia in subsequent admissions. Of the subjects who did not develop MIDi, 53 (17.3%) demonstrated hyperglycemia at some point during follow-up. However, all these episodes were related to treatment following relapse, bone marrow transplant or febrile neutropenia, and therefore were not included in the analysis.

Eleven subjects (19.3%) in the MIDi group required insulin during induction. Six subjects required insulin during additional cycles of treatment. No episodes of diabetic ketoacidosis were observed. None of the subjects required insulin after completion of therapy.

### Multivariate analysis

The multivariate model can be seen in Table 2. On multivariate analysis, age greater than or equal to 10 years and the presence of CNS disease at diagnosis were significantly associated with the development of MIDi. When adjusted for the effects of age, gender and CNS disease at diagnosis, the presence of Trisomy 21 was not associated with MIDi.

We did not include the three-drug versus four-drug induction variable in the final multivariate regression model, as it was highly correlated with the age variable (Pearson chi-square 95.7, $P<0.001$). We also did not include death in the final model, as although this was significantly associated with MIDi it was our objective to look at predictors of MIDi and since death occurred later it could not be considered a risk factor.

## Discussion

The cohort described in this study is one of the largest cohorts investigated for patient, treatment and disease related risk factors for MIDi in a pediatric setting. A number of studies have described MIDi in pediatric ALL (Table 3).

The prevalence of MID during remission induction in our cohort (15.6%) is similar to that found in previous studies [11, 12]. Pui et al. [16] and Baillargeon et al. [10] reported lower rates in the range of 10 to 11%. The study by Pui et al. was performed in the early 1980s, when there may have been a different prevalence of the risk factors that have been associated with this condition including obesity and ethnic background. Sonabend et al. reported an extremely high prevalence of hyperglycemia during remission induction. This may be attributed to the fact that blood glucose levels were measured postprandially and a single

**Table 1** Demographic, disease and treatment characteristics of the study subjects

| Characteristic | Study population | Number (%) with MIDi | OR (95% CI) | *P* value |
|---|---|---|---|---|
| MIDi | | | | |
| No | 306 (84.3%) | | | |
| Yes | 57 (15.7%) | | | |
| Gender | | | | |
| Male | 222 (61.2%) | 35 (15.8) | 1.0 (0.6–1.8) | 0.967 |
| Female | 141 (38.8%) | 22 (15.6) | | |
| Age group at diagnosis of ALL (years) | | | | |
| <10 | 288 (79.3%) | 23 (8.0) | 9.6 (5.1–17.8) | <0.001 |
| ≥10 | 75 (20.7%) | 34 (45.3) | | |
| BMI[a] | | | | |
| Normal weight (BMI<85%) | 256 (70.5%) | 42 (16.4) | 1.0 (−) | |
| Overweight (BMI 85%–95%) | 47 (12.9%) | 7 (14.8) | 0.9 (0.4–2.2) | 0.887 |
| Obese (BMI≥95%) | 36 (9.9%) | 8 (22.2) | 1.4 (0.6–3.3) | 0.432 |
| Trisomy 21 | | | | |
| No | 350 (96.4%) | 52 (14.9) | 3.6 (1.1–11.4) | 0.030 |
| Yes | 13 (3.6%) | 5 (38.5) | | |
| WBC at diagnosis of ALL[b] | | | | |
| WBC≥$50\times10^9$/L | 53 (19.0%) | 13 (24.5) | NS | 0.242 |
| WBC<$50\times10^9$/L | 226 (81.0%) | 40(17.7) | | |
| Steroid used during induction[c] | | | | |
| Prednisone | 284 (78.2%) | 46 (16.2) | 0.9 (0.4–1.8) | 0.683 |
| Dexamethasone | 77 (21.2%) | 11 (14.3) | | |
| Number of drugs used during induction | | | | |
| 3 | 192 (52.9%) | 11 (5.7) | 6.1 (3.0–12.2) | <0.001 |
| 4 | 171 (47.1%) | 46 (26.9) | | |
| CNS disease at diagnosis | | | | |
| No | 345 (95%) | 50 (14.5) | 3.8 (1.4–10.1) | 0.009 |
| Yes | 18 (5%) | 7 (38.9) | | |
| Death | | | | |
| No | 333 (91.7%) | 47 (14.1) | 3.0 (1.3–6.9) | 0.008 |
| Yes | 30 (8.3%) | 10 (33.3) | | |

*MIDi* medication induced diabetes during induction

*CNS* central nervous system, *NS* non-significant, *ALL* acute lymphoblastic leukemia, *BMI* body mass index, *WBC* white blood cells

[a] Twenty-seven patients, aged under 2 years, were not included in BMI calculation

[b] WBC results were available for 279 patients

[c] Two subjects with unknown induction steroid are not included

**Table 2** Multivariate logistic regression analysis of the risk factors for the development of MIDi

| Risk factor | OR (95% CI) | *P* value |
|---|---|---|
| Gender | 0.8 (0.4–1.6) | 0.566 |
| Age≥10 years | 10.5 (5.4–20.2) | <0.001 |
| CNS disease at diagnosis | 5.1 (1.6–16.1) | 0.006 |
| Trisomy 21 | 3.7 (0.9–14.8) | 0.062 |

*CNS* central nervous system, *OR* odds ratio, *CI* confidence interval

measurement of glucose greater than 200 mg/dL was sufficient to be included in the study group [13]. In addition, this cohort included a very high proportion of patients with Hispanic background who are known to have a different metabolic profile than Caucasians. It may be that some of these patients were at increased risk for type 2 diabetes mellitus (DM), which was unmasked by the addition of steroids. The hyperglycemia seen in that population may be related, in part, to a genetic predisposition to type 2 DM inherent in this group, as opposed to the medication induced diabetes described in other populations.

**Table 3** Previous studies on medication induced diabetes during induction (MIDi)

| Investigator | Year | Number of subjects | Number (%) with MIDi | Risk factors for MIDi | Notes |
|---|---|---|---|---|---|
| Pui et al. [16] | 1981 | 421 | 39 (9.7) | Age>10 years, obesity, family history, Down syndrome | St. Jude Children's Hospital |
| Baillargeon et al. [10] | 2005 | 155 | 17 (11) | Age, BMI, female gender, family history | Patients of Hispanic descent. South Texas |
| Roberson et al. [12] | 2009 | 871 | 141 (16) | Older age | St. Jude Children's Hospital. MIDi not associated with remission rates, event free survival or overall survival |
| Lowas et al. [11] | 2009 | 161 | 33 (20.4) | Age>10 years, BMI>85th %ile, native L-asparaginase | Portland, Oregon |
| Sonabend et al. [13] | 2009 | 161 | 56 (34) | Older age, BMI>85th %ile, prednisone | Texas Children's Hospital. Hyperglycemia during induction associated with decreased relapse free survival and increased risk of death |

Our findings confirm that older age is associated with an increased risk for the development of MIDi. This is in agreement with a number of previous studies that demonstrated odds ratios of 2.3–37.2 when comparing the risk of developing hyperglycemia during induction in children aged 10 years and older in comparison to younger children [10–13]. This finding may be related, in part, to the hormonal milieu of puberty which is characterized by higher growth hormone levels and increased insulin resistance. Older age is associated with a worse prognosis in patients with ALL. We were not able to assess whether the increased prevalence of hyperglycemia in this age group plays a role in the poorer prognosis, and this may be examined in future prospective studies.

BMI has been described as a risk factor for the development of MID. Baillargeon et al., Sonabend et al. and Lowas et al. all described the overweight state (BMI>85th percentile) as a risk factor [13, 16].

In our study, we examined BMI percentile as a continuous variable, as well as dividing the cohort into weight categories. In contrast to many of the studies in this area, we did not find an association between BMI and MIDi in our cohort. Recently, Amed et al. conducted a survey of secondary diabetes in the pediatric population in Canada [20, 21]. They reported that children with MID were less likely to be overweight than children with type 2 DM. In fact, the prevalence of overweight in our cohort in general and in the MIDi group specifically was not different from that in the general population in Canada which is known to be 23% [22]. This observation supports our hypothesis that factors other than BMI may be more important contributors to the development of MIDi. The hyperglycemia seen in the context of glucocorticoid therapy in obese patients may be related to a different process than the MIDi seen in normal weight individuals. For example, it is possible that those with obesity and its inherent underlying insulin resistance decompensate with exaggerated insulin resistance caused by glucocorticoid therapy. At the same time, those with lower BMI who develop MIDi may have an underlying defect in beta cell insulin secretion that is unmasked by the use of steroids. It is possible that in the cohorts with a higher prevalence of obesity and at risk ethnic groups a proportion of the hyperglycemia seen is related to unmasking of type 2 DM, which is highly associated with obesity, following addition of glucocorticoids. It is not possible to test this hypothesis in our study, but it would be worthwhile to examine these patients prospectively for abnormal glucose tolerance later on. Our findings showing no association with increased BMI suggest that we may be identifying a subgroup of children that are different from the more "typical" obese children at risk for future type 2 DM.

MIDi has been shown in previous studies to be more prevalent in patients with Trisomy 21 [16]. Individuals with Trisomy 21 have a higher prevalence of type 1 and type 2 DM and therefore may have a higher underlying risk for both insulin resistance and beta cell dysfunction. Our findings are consistent with this observation but did not reach statistical significance, possibly due to the small number of subjects with this condition in both groups.

We found that CNS involvement at the time of diagnosis was associated with the development of MIDi even after adjustment for a number of potential confounding variables. Since glucose levels were not routinely measured on admission, we did not examine whether these patients presented with higher glucose levels. Doses of glucocorticoids and L-asparaginase given as part of remission induction in this group did not differ from the remainder of the cohort who received similar protocols. We are not aware of data that could explain this finding.

In patients with ALL, secondary diabetes during induction has been associated with shorter remission intervals, increased overall mortality and increased risk for developing complicated infections [8]. These findings were first reported in adults by Weiser et al. [23] but are difficult to extrapolate into the pediatric population because of the presence of co-morbidities that are frequently seen in adults with cancer. Sonabend et al. reported a poorer relapse free survival in patients with MIDi and poorer overall survival after 6 years of follow-up [13]. Roberson et al., however, failed to demonstrate any difference in remission, event free survival, overall survival or cumulative incidence of relapse in their cohort [12]. We did not see an association between MIDi and relapse or need for bone marrow transplantation. We did, however, observe an increased prevalence of death in the patients who developed MIDi. ALL therapy occurs over a number of years, and therefore many variables influence the outcome of treatment. Risk factors such as specific molecular markers, CNS involvement and response to induction, among others, have been established as important predictors of outcome [24, 25]. A detailed assessment of these markers and the role that the presence of MIDi may play in the ultimate outcome of therapy was beyond the scope of this study.

Our study has several limitations: Due to its retrospective nature, some potentially useful data, such as ethnic background and family history of diabetes and the metabolic syndrome, were not available. The number of overweight and obese patients who developed MIDi was small which may have led us to miss a potential association between BMI and the development of MIDi. Although all patients received standard morning glucose measurements, follow-up glucose checks were performed on a clinical basis and were not always available at similar time points. In addition, the management of hyperglycemia varied significantly between different treating physicians, impairing our ability to assess treatment efficacy. In order to assess the optimal way to manage patients with MIDi in this population, a prospective study, with a uniform protocol would be needed. Although all patients received the same chemotherapeutic agents, these were given according to a number of different protocols with varying doses and schedules. Many of the protocols were only used for a few patients. It was therefore not possible to assess the effect of any particular protocol or drug on the development of medication induced diabetes during induction. We were able to look at the effect of prednisone vs. dexamethasone and, we did not find any difference between the two medications. This finding is not surprising, since doses of the two drugs were of similar glucocorticoid effect [14]. Unfortunately, we did not examine data regarding tumor lysis syndrome (TLS) or the presence of infection during induction in our cohort. However, from previous research in a similar cohort, we know that the risk of TLS during induction is 23% and the risk for microbiologically proven infection is 19.5% [26, 27].

The findings of this study indicate that children 10 years of age and older and those with CNS involvement are at increased risk for the development of MID during remission induction. Elevated BMI was not a risk factor in our cohort. As is the usual practice, it is important to monitor glucose levels in patients receiving therapy for ALL. A high level of suspicion should be maintained in older children, those with Trisomy 21 and those presenting with CNS disease. In some populations, patients with a higher BMI may be at increased risk for hyperglycemia. Further prospective studies may help with our understanding of the etiology of this condition, especially in certain ethnic groups and in those children who are overweight.

**Conflict of interest** The authors have no conflict of interest to declare.

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