Drug induced Diabetes Mellitus (DIDM) in Pediatric Acute Lymphoblastic Leukemia (ALL): Approach to diagnosis and management

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Abstract

Corticosteroids and L-asparaginase used in the treatment of pediatric acute lymphoblastic leukemia (ALL) results in Drug induced Diabetes Mellitus (DIDM). Literature on the management of DIDM among children with ALL is sparse and the diagnostic criteria for pediatric diabetes should be carefully applied considering the acute and transient nature of DIDM during ALL therapy. Insulin remains the standard of care for DIDM management and the choice of Insulin regimen (standalone Neutral Protamine Hagedorn (NPH) or basal bolus) should be based on the type and dose of steroids used for ALL and the pattern of hyperglycemia. A modest glycemic control (140-180 mg/dl) to achieve euglycemia and prevent hypoglycemia would be the general approach. This review is intended to suggest a evidence based practical guidance in the diagnosis and management of DIDM during pediatric ALL therapy.

Introduction

Current survival outcomes of pediatric acute lymphoblastic leukemia (ALL) approaches 90% in high income countries(1). Improved survival in childhood ALL results from a fine balance between the utilization of intensified chemotherapy protocols and rigorous supportive measures to address complications arising during therapy(2). Drug induced diabetes mellitus (DIDM) is a common complication during ALL treatment and the reported prevalence of which varies between 9.7% to 69% in literature(3). Older age (Age>10years), obesity (BMI[?]+2), Trisomy 21, high risk ALL group are well known risk factors for the occurrence of DIDM in ALL. Complications of DIDM during ALL therapy include diabetic keto-acidosis, higher risk for infections, including cellulitis, bacteraemia, fungaemia and a higher incidence of febrile neutropenia(4). The impact of hyperglycaemia on overall outcomes in ALL is mixed. Analysis of four consecutive pediatric ALL clinical protocols (1991 to 2007) from St. Jude's children research hospital found no significant difference in clinical remission rates, event free/overall survival, cumulative incidence of relapse and probability or types of infection between patients who did and did not experience hyperglycaemia(5). However, a recent study from North America noticed that, patients developing DIDM during induction chemotherapy were more likely to require admission to intensive care unit and increased mortality. These patients are also more likely to have subsequent serious infections, greater length of hospital stay, disease relapse, transplant need and higher cost of care(6). Majority of the evidences for management of DIDM during ALL therapy arises out of retrospective studies and there are no clear-cut guidelines for the diagnosis and treatment of DIDM during ALL treatment(7). The purpose of this review is to provide a constructed approach for diagnosis and management of DIDM in paediatric ALL.

Pathogenesis of DIDM during ALL therapy

Occurrence of DIDM during ALL therapy has been mainly attributed to chemotherapeutic agents like L-asparaginase and corticosteroids(8)(9)(10). However, diabetogenic effect of leukemic process affecting glucose homeostasis has also been hypothesised to cause DIDM in ALL patients. Corticosteroids such as dexamethasone and prednisolone induce DIDM by damaging pancreatic beta cells, reducing insulin production, increasing insulin resistance, stimulating gluconeogenesis and lipolysis, and increasing counter regulatory hormones such as glucagon and adrenaline(3). Corticosteroids reduce the expression of glucose transporter 2 and glucokinase while increasing the activity of glucose-6-phosphate dehydrogenase(11)(12)(13). Also, corticosteroids stimulate the apoptosis of pancreatic beta cells by repressing the anti-apoptotic protein B-cell lymphoma 2, and by activating calcineurin(3). Type of corticosteroids (dexamethasone Vs prednisolone) doesn't seem to influence the occurrence of DIDM during ALL therapy(14)(15), however the dose and duration of corticosteroids administration may impact DIDM (supplementary file, Table-1). L-asparaginase acts by depleting L-asparagine which may lead to decreased insulin synthesis and secretion. It has also been shown to increase the insulin resistance possibly by inducing conformational change and depletion of insulin receptors(16). Direct toxic effect of L-asparaginase resulting in pancreatitis may in turn cause DIDM. Native L-asparaginase is associated with higher risk of DIDM in ALL patients compared to PEG-L-asparaginase(17). Dose and schedule of L-asparaginase administration may also affect the incidence of DIDM during ALL therapy. Treatment with corticosteroids and L-asparaginase in combination synergistically increases glucose intolerance and DIDM(18). Impaired glucose tolerance can lead to immune dysfunction predisposing ALL patients to severe infections. Poor outcomes in ALL patients with DIDM associated altered metabolism that supports the proliferative state of leukemic cells, is an area of active research(19).

Management of Drug induced Diabetes Mellitus (DIDM) during ALL therapy

There is a lack of standard guidelines or recommendations on the management of DIDM in children on ALL directed chemotherapy. Based on the available data and information in the literature to the best of our knowledge, we have formulated a comprehensive and well-defined clinical care approach towards the diagnosis and treatment of DIDM in children on ALL directed chemotherapy. A simplified flow-chart is presented in Table-1.

Diagnosis of DIDM during ALL directed chemotherapy

Diagnostic criteria used in literature for DIDM /hyperglycemia varies significantly with cut offs used, timing of test, number of abnormal tests used for diagnosis(20)(15)(21)(22). However, as per the most recent pediatric diabetes guidelines, diagnosis of DIDM is not different from Diabetes mellitus (DM) due to any other etiology (23)(24). Nevertheless, these criteria should be carefully applied considering the pharmacology of the offending drug, pathogenesis of DIDM and taking into account of its transient nature.

Measurement of fasting glucose alone will underestimate the incidence of DIDM when on intermediate acting glucocorticoids (prednisolone, methyl prednisolone) as a single morning dose considering their peak (4-6 hours) action and duration of action (12-16 hours). In such instances, measuring post lunch and/or pre dinner blood sugar values would be useful. When long acting glucocorticoids (Dexamethasone) or intermediate-acting glucocorticoids in divided doses are used post-lunch, pre-dinner and fasting glucose values would be helpful for diagnosis. Utility of oral glucose tolerance testing is limited in diagnosing DIDM during ALL treatment due to practical difficulty in conducting the test. Similarly, HbA1c is also not useful considering the acute onset of DIDM(25)(26). Hence post-lunch and/or pre-dinner glucose level [?] 200 mg/dl, when on intermediate-acting glucocorticoids as single morning dose and additional fasting glucose [?] 126 mg/dl when on long-acting steroids or intermediate acting steroids in divided doses are most useful for diagnosing glucocorticoid induced Diabetes Mellitus. For L-asparaginase induced Diabetes mellitus, random sugar value of [?]200 mg/dl, can be used for diagnosing DIDM as there is no fixed pattern of hyperglycemia seen. It is imperative to confirm the diagnosis by repeat testing in the absence of unequivocal hyperglycemia(23)(24).

Monitoring for the development of DIDM during ALL directed therapy

It is important to plan screening and monitoring blood sugars taking into consideration the potency of steroids used, its dose, duration and peak action, dosing schedule, individual risk to develop DIDM, concomitant usage of other drugs which can synergistically result in DIDM.

Prednisolone, an intermediate-acting glucocorticoid when used as single morning dose likely to result in post lunch and night time hyperglycemia matching their peak (4-6 hours) and duration of action (12-16 hours). However, prednisolone when administered in divided doses can cause persistent hyperglycemia throughout the day with post prandial peak. Dexamethasone a long-acting steroid (duration of action >24 hours) will result in persistent hyperglycemia throughout the day with a slight decline after an overnight fast (25)(26)(27)(28).

Steroid induced hyperglycemia is known to occur acutely and transiently. Hence Endocrine Society guidelines on management of hyperglycaemia in earlier non-diabetic, non-critically ill hospitalised patients on steroid therapy advocates discontinuation of monitoring after 24-48 hours if all measured blood glucose values are normal(29)(30). But a recent study conducted in children with ALL noticed that, during Induction phase hyperglycemia can develop anywhere between first to fifth week after initiation of steroids(31). Similarly, non-diabetic adults with ALL on steroid therapy were shown to have hyperglycemic episodes between 2-4 weeks after initiation of induction chemotherapy(32). These findings were replicated in other studies involving adults, secondary to glucocorticoid exposure in non ALL settings(33)(34)(35). Diabetes Mellitus secondary to L-asparaginase occurs mostly within first week of initiation of treatment(36)(21)(37). Recently, PEG L-asparaginase usage in ALL has reduced the incidence of DIDM from 25% to 5-7 %(37).

Monitoring for DIDM should begin with documentation of baseline blood glucose levels before initiation of chemotherapy. We suggest glucose measurement for 2-3 days per week in all children on ALL directed chemotherapy (post lunch and/or pre dinner glucose when on intermediate-acting glucocorticoids as single morning dose and additional fasting glucose when on long-acting steroids or intermediate-acting steroids in divided doses) to diagnose DIDM throughout the period of steroid therapy, in addition to close watch for hyperglycemic symptoms. When on L-Asparaginase alone (without steroids), we suggest 2 to 3 random glucose testing routinely in the first week, followed by as and when required in case of hyperglycaemic symptoms, until completion of therapy.

We suggest the screening, diagnosis and treatment optimization using bedside Point Of Care (POC) capillary glucose monitoring (29). Diagnostic accuracy of POC meters should be at least 20% of real values(38). Due consideration to variables that can affect POC glucometer functioning like site and procedure of testing, high or low haemoglobin levels, low tissue perfusion and interaction with extraneous substances should be considered before interpreting values(39).

Treatment for DIDM in during ALL directed therapy

In view of potential adverse effects of hyperglycaemia, all children on ALL directed therapy who fits into the diagnostic category would need prompt initiation of treatment. Generally, offending drugs are not reduced or stopped, instead treatment of hyperglycaemia to be optimised(40)(3). Considering the heterogeneity of factors that affect the development of DIDM in ALL, treatment strategy should be individualised. Treatment considerations for DIDM in ALL may include non-pharmacologic and pharmacologic measures.

Non-pharmacologic treatment

Non-pharmacologic treatment such as use of dextrose free fluids and dietary management should be first thing to be considered as soon as the diagnosis of DIDM is entertained, unless patient is unstable and/or has metabolic derangements due to severe hyperglycemia. Dietary changes should focus on optimizing the amount and type of carbohydrates (avoid simple sugars and increase proportion of complex carbohydrates), taking care of the caloric needs of the child to maintain adequate weight during therapy. Challenges specific to ALL patients i.e., poor appetite, catabolic state, treatment induced gastritis/gastro esophagitis should be addressed whenever possible.

Pharmacological treatment

Insulin Therapy:

Insulin is the treatment of choice for DIDM secondary to glucocorticoids and L-asparaginase(29)(36). It is suggested to begin insulin therapy once diagnosis of DIDM is entertained. Table-2 (supplementary file) enlists different types of insulin, onset, peak and duration of action after subcutaneous injection. Children presenting with or developing DKA should be managed with the existing standard guidelines for acute management with intravenous fluids and insulin infusion(41). It is prudent to document pattern of hyperglycaemia and tailor made the therapy. Insulin regimen, dose, and duration should be guided by pattern of hyperglycaemia, child's age and the severity of metabolic derangements.

Stand Alone Basal Insulin:

Whenever Intermediate acting steroids are used as a single morning dose, resultant hyperglycaemia is known to increase as the day progresses, peaking post lunch, slowly settling by night. Hence, a single morning dose of Neutral Protamine Hagedorn (NPH), which has similar pharmacokinetic (peak action 4-8 hours, duration of action 12-16 hours) profile as that of intermediate acting steroids will best suit this scenario(42)(25). Clore et al(42) used a weight and steroid dose dependent algorithm in adults, using NPH insulin based on known dose-response effects of glucocorticoid on insulin sensitivity and their empiric observation over 5years. They found 0.4 U/kg, 0.3 U/kg, 0.2 U/kg, 0.1 U/kg of NPH for prednisolone [?] 40 mg/day, 30 mg/day, 20 mg/day, 10 mg/day respectively resulted in excellent glycaemic control. Hence, in the absence of vast experience it is suggested to begin with similar dose of NPH in children in this scenario.

Single dose, patient comfort, easy titration are advantages of this regimen. However, in case of persistent hyperglycaemia, an increase in the dose of morning NPH and/or additional prandial regular/rapid acting insulin would be required.

Basal Bolus Insulin:

This insulin regimen is useful in case of persistent hyperglycaemia, resulting secondary to long-acting glucocorticoids or intermediate-acting glucocorticoids in divided doses. Usual dose of insulin used in children with Type 1 DM ranges from 0.7-1 U/kg/day (pre pubertal children) to 1-2 U/kg/day (pubertal children). As insulinopenia in DIDM is not expected to be as severe as in Type 1 DM, a lower cumulative dose may be required. However, exact insulin doses to be used in the settings of DIDM among children on ALL directed chemotherapy is not known. In a recent review by Pasqel FJ et al(43), a starting dose of 0.3-0.5 U/kg/day insulin, for basal bolus regimen in hospitalised adult patients with new onset hyperglycaemia is suggested. We suggest to use similar lower dose in children to start with and titrate slowly based on desirable target glucose. Pubertal children and those with insulin resistance may need steep escalation of dose. In this scenario, 25-50 % of basal insulin with 50-75 % of bolus insulin is usually suggested. Higher bolus insulin than usual may be required to compensate for post prandial surge in glucose. Commonly NPH is used as basal insulin, however glargine can also be used especially with dexamethasone (25)(44).

This regimen necessitates close watch for hypoglycaemia, frequent POC glucose monitoring, insulin dose adjustment based on pre-prandial glucose and insulin sensitivity factor, and involvement of parents. However, chance of optimal glucose control is higher in this regimen.

Prandial insulin:

In this regimen, short acting/ rapid acting insulin is used to curtail post prandial glucose surge secondary to defective post prandial insulin secretion. Regular insulin, 0.1 U/kg/dose (for people who eat snack in between meal) or rapid acting insulin (for people who do not eat snack in between meal) is used with each meal. Additional supplemental dose is used based on pre-prandial glucose levels and insulin sensitivity factor. Persistent elevation of pre-prandial glucose beyond the target necessitates increase in previous insulin dose. However, this scheme doesn't account to progressive increase in insulin resistance which is often seen and not suitable when hyperglycaemia is persistent throughout the day. As of now no study has demonstrated that post-prandial defective insulin secretion as the only mechanism of hyperglycaemia, hence this strategy is often questioned and not suitable in many instances(42). Utility of standalone insulin pumps or insulin

pumps with Continuous Glucose Monitoring Systems (CGMS) is limited considering scarcity of data and concerns about general wellbeing of children with leukaemia.

At present, there are no studies to prove superiority of one regimen over other. Considering mechanism of glucocorticoid induced hyperglycaemia, pharmacokinetics of steroid and insulin, it is reasonable to use NPH alone in the presence of predominant post lunch hyperglycaemia with falling glucose levels by the end of the day. Similarly, basal bolus regimen is preferable in the presence of persistent hyperglycaemia throughout the day with long acting steroid or intermediate acting steroid in divided doses.

Monitoring while on insulin therapy, glycaemic control targets, dose modification:

After initiation of insulin therapy, all pre-meals and bed-time glucose measurements should be done routinely. In addition, post-meal glucose values give idea about adequacy of bolus insulin. Experience with CGMS in acute hospital setting is scarce, more so with children. Also acute physiological state (dehydration, catabolic state, infection) of children with ALL raises concerns about the accuracy of CGMS. Close watch for hypoglycaemia symptoms and monitoring with POC testing to pick up hypoglycaemia throughout duration of insulin therapy is mandatory. Prompt treatment of hypoglycaemia should be done as per standard protocols and necessary change in the dose of insulin should be made if necessary(45).

As DIDM is known to be transient in majority of cases, intention of treatment is largely to reduce acute metabolic complications and improve outcome of ALL directed therapy. Hence a tight control of glucose is not always mandated in contrast to Type 1 DM. Also, tight glucose control comes with the risk of hypoglycaemia especially in young children. After NICE-SUGAR trial(46) ADA has recommended glycaemic targets of 140-180 mg/dl in critically ill and non-critically ill hospitalised adult patients with diabetes(43)(47). We suggest to follow the same cut offs in children on ALL directed chemotherapy with DIDM than strict glucose control targets used in Type 1 DM(47).

In addition to bolus insulin, supplemental prandial bolus insulin (correction bolus for elevated pre-meal blood sugar) to be administered based on Insulin Sensitivity Factor and pre-meal blood glucose. Correction bolus is calculated by dividing 1500 (1800 in case of rapid acting insulin) by total daily insulin dose, to get the mg/dL of glucose that is lowered by 1 unit of regular insulin(48).

Insulin doses have to be titrated to achieve target glucose. Based on POC capillary blood glucose values over 2-3 days, basal and bolus insulin dose can be adjusted up to 15-20 % at a time(49). So, detailed glucose profiling while on insulin treatment is very useful to monitor, titrate and optimise the treatment. Changes in dose of glucocorticoid mandates the necessary change in insulin dose. Roughly, 50% of change in glucocorticoid dose (increase or decrease), should follow 25 % change in insulin dose.

Most of the time, hyperglycaemia settles within 2 days of stopping steroids(25), hence majority of the cases can be discharged without insulin. In case of continuing insulin therapy, necessary diabetic education to be provided to parents for domiciliary management(49)(50).

Non-Insulin pharmacological treatment

Though insulin is the mainstay of treatment of DIDM, other pharmacological agents has been tried in the past with variable success. Metformin has been suggested to be safe and reasonably effective in a retrospective analysis (51) where 17 children with DIDM on ALL directed therapy, required metformin for median 6 days (range-246 days), with dose ranging from 100-2000 mg/day. Twelve patients didn't require insulin for sugar control. Seelig E. et al(52) in their randomized controlled trial on adult patients receiving steroids for various indications showed normally maintained median glucose by 2- hour area under curve (AUC) during oral glucose tolerance test after 4 weeks of steroid therapy along with metformin unlike control patients. Another recent trial(53) demonstrated metformin could prevent dysglycemia in adults with cancer. So, metformin looks an attractive alternative/addition to insulin, as it is not associated with discomfort of pricks by insulin administration and sugar monitoring lancets, with reduced risk of hypoglycemia. In addition, advantages not related to glycemic control has been suggested i.e. beneficial effect in malignancy due to m-TOR inhibition and protection from anthracycline cardiotoxicity(54)(55)(56). Limitations of metformin administration for

hyperglycemia management in ALL are lack of strong evidence of efficacy, difficulty in rapid titration of doses as per sugar levels and concerns regarding its side effect profile in critically ill children. Further larger prospective studies are necessary to address these concerns.

Recently, Glucagon Like Peptide-1 (GLP-1) agonist, exenatide has been shown to be effective in prevention of steroid induced glucose intolerance and beta cell dysfunction in healthy adults (57). More evidence is required to use this drug in drug induced hyperglycemia setting. Other oral antidiabetic drugs i.e. sulfonylureas, thiazolidinediones, DPP-4 inhibitors, meglitinides etc. has been tried in adults with steroid induced hyperglycemia. But use of these drugs in DIDM during pediatric ALL therapy has not been approved, so detailed discussion in context of DIDM is beyond the scope of this article.

Conclusion

Prompt monitoring for hyperglycemia is suggested for early diagnosis and treatment of DIDM among children with ALL on corticosteroids and L-asparaginase. Elevated fasting ([?]126 mg/dl) or post lunch ([?]200 mg/dl) POC glucose is the suggested criteria for diagnosis of DIDM. Insulin is the treatment of choice for DIDM, while insulin regimen to be chosen based on the pattern of hyperglycemia. While on insulin frequent blood glucose monitoring and dose titration to achieve target sugar levels (140-180 mg/dl) and watch for hypoglycemia is suggested. Treatment options other than insulin are generally not suggested for DIDM in pediatric ALL setting.

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