RESEARCH ARTICLE

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The influence of patient variables on insulin total daily dose in paediatric inpatients with new onset type 1 diabetes mellitus

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Abstract

Purpose Insulin dose requirements at new diagnosis of type 1 diabetes mellitus (T1DM) vary widely. Current guidelines recommend an initial total daily dose (TDD) ranging from 0.5 to 1.0 IU/kg/day. It often takes several days of frequent dose adjustments before an optimal insulin dose is achieved. The aim of this study was to identify the influence of patient variables on the dose-requirement of insulin in newly diagnosed children with T1DM.

Methods A retrospective chart review of children (≤ 18 years old) admitted to hospital between 2010 and 2016 due to new onset T1DM was undertaken. Demographic, clinical, insulin dosing, and laboratory data were recorded. The influence of patient characteristics on insulin TDD was analysed statistically by performing univariate and multivariate linear regression analyses.

Results Complete clinical records for 70 patients were available for analysis. The median insulin TDD on first day of admission was 21 (4.5 to 75 units) and that on the day before discharge was 27 (5.5 to 124 units). In the multivariate regression analysis, body size (total body weight and fat-free mass), glycated haemoglobin (HbA1C), and blood ketone concentration were found to be significant predictors of optimal insulin TDD ($p < 0.05$).

Conclusion In addition to body size, HbA1c and ketone concentrations are useful in calculating initial TDD in newly diagnosed children with T1DM. This could potentially decrease the number of days needed to reach a stable dose and result in improved early glycaemic control.

Keywords Insulin dose · Covariates · Paediatrics · Blood glucose

Introduction

In recent decades there have been considerable advances in both the treatment and monitoring of type 1 diabetes (T1DM) in children. These include improvements in insulin delivery and glucose monitoring technologies, such as insulin pump therapy and continuous glucose monitoring [1]. However, many questions remain regarding optimal management, and manifest in considerable variation in practice, often in areas that on first glance would appear straightforward. One such example is insulin regimen where variation exists both within and between countries [2, 3].

Variation in clinical practice is not limited to insulin dosing regimen with recent work showing variable initial starting doses of insulin in children and adolescents [2]. This is reflected in the major practice guidelines, which lack consensus on the optimal insulin starting dose in children with new onset T1DM. According to the International Society for Paediatric and Adolescents Diabetes (ISPAD), the starting dose for pre-pubertal children ranges from 0.7–1.0 IU/kg/day [4]. The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) guidelines recommend initial insulin doses of 0.4 to 0.5 units/kg/day whereas the American Diabetes Association (ADA) recommends that the initial totally daily dose (TDD) for children and adolescents varies between 0.5 to 1.0 IU/kg [5, 6].

Clearly, insulin dosing is complex and various patient factors play a role in determining insulin dose

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requirements [7]. These factors include patient age with puberty, and associated sex steroids and growth hormones, being associated with a decrease in insulin sensitivity with subsequent increase in insulin dose requirements [4, 8–11]. Another prominent factor is sex with higher TDD reported in females between the ages of 3 and 13 years and higher TDD in males between the ages 14 and 18 years [12]. Various other patient factors have been reported to influence insulin sensitivity including vitamin D status [13, 14], B-lymphocytes and thyroid function [15, 16], and the occurrence and severity of diabetes ketoacidosis (DKA) at diagnosis, which may reflect very low concentrations of circulating endogenous insulin.

All these influencing factors on insulin and glucose metabolism may reflect a high variability in insulin dose requirements. Most of these variables are measured clinically and it would be of interest to explore their influence on insulin dose and potentially to use these in insulin dose individualisation.

The aim of this study was to assess the influence of patient characteristics and clinical variables on the dose-requirement of insulin in newly diagnosed children with T1DM.

Methods

Study population and design

This study included children (≤ 18 years old) who were admitted to Dunedin Public Hospital in New Zealand between December 2010 and December 2016 due to new onset T1DM. Dunedin Public Hospital is the tertiary paediatric endocrinology referral centre for the southern portion of New Zealand. Approximately 180 children with diabetes of various forms live in this large geographical region (~80,000 km^2). Due to this geography, only approximately 12–15 new paediatric presentations of diabetes are seen at the Dunedin Hospital site each year, and are all managed in an inpatient setting. Insulin daily dose is determined initially based on patient weight. Subsequently, the dose is adjusted based on blood glucose measurements and carbohydrate intake until normal blood glucose concentrations (BGC) and stable insulin doses are reached. Glycaemic targets in the outpatient setting are blood glucose of 4–8 mmol/L, and HbA1c of <55 mmol/mol, but discharge following new diagnosis occurs once diabetes and carbohydrate counting education is complete, with further insulin adjustments made on an outpatient basis.

The study was a retrospective chart/electronic database review of Dunedin Hospital admissions. Relevant admissions were identified through the paediatric diabetes service at Dunedin Hospital. The inclusion criteria were: diagnosis of T1DM confirmed by autoantibody status (islet antigen 2 antibody (IA2), glutamic acid decarboxylase 65 autoantibody (GAD), or islet cell cytoplasmic autoantibody (ICA)); age less than or equal to 18 years; and initial insulin treatment at Dunedin hospital.

The clinical notes were reviewed and patient details were summarised. The following data were recorded for each patient: age; sex; ethnicity; weight; height; blood pH and bicarbonate concentration; glycated haemoglobin (HbA1c) concentration (Bio-Rad D100, cation exchange HPLC automated testing system); blood glucose concentration (BGC); blood ketone (β-hydroxybutyrate) concentration; 1,25-dihydroxyvitamin D concentration; creatinine concentration; antibody status (IA2 and GAD); thyroid hormone concentration (TSH and T4); lymphocyte blood concentration; and any concomitant medication with focus on drugs that may affect blood glucose (e.g. steroids). Additionally, the patient's subcutaneous (SC) insulin doses and dosing times were recorded throughout their hospital stay.

The total daily dose was calculated by adding short and long acting insulin doses which were administered between 0 and 24 h on the first day and last day of admission. Based on weight, height, age, and creatinine blood concentration, body surface area (BSA) [17], fat free mass (FFM) [18], and creatinine clearance [19, 20] were calculated. FFM has been shown to correlate better with the rate of body metabolism and may potentially be a better predictor of insulin dose requirements than weight [18], especially given the rise of obesity rates in children with type 1 diabetes [21].

Statistical analysis

Univariate analysis was used to screen covariates for significance at the $p < 0.2$ level. Covariates with a p value of <0.2 in the univariate analysis were used in a multivariate linear regression analysis to identify predictors of the difference in TDD at the $p < 0.05$ level of significance using a step-wise approach. Statistical analysis was carried out using STATA v14.1 (StataCorp 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

TDD on the last day of admission was used as the dependent variable for the regression analysis. For patients who required insulin infusions at the beginning of their hospital stay due to DKA, the days of insulin infusions were excluded.

For each covariate, data from the first day of admission was used. For BGC and blood ketone concentration, the highest values within the first 5 h of admission were chosen. In cases where the patient's height wasn't recorded, the height on date of admission was extrapolated from later measurements by identifying the patient's percentile using the world health organisation (WHO) growth charts.

Ethics approval

The study was approved by the University of Otago Human Ethics Committee (HD16/013) and in accordance with Declaration of Helsinki.

Results

Seventy children admitted with new onset T1DM were included in the analysis. The diagnosis was confirmed by either positive GAD (69/70) or positive ICA (1/70). Of the 70 patients, 24 were admitted with DKA as defined by ISPAD criteria (pH <7.3 and/or bicarbonate concentration < 15 mmol/L) [22]. Patients' demographic, clinical characteristics, and clinical measurements are summarised in Table 1 below.

Physicians and diabetes nurse specialists assessed glycaemic control of the children by the results of blood sugar measurements during their admission and adjusted insulin dosing accordingly. Patients were discharged once education was complete, and good glycaemic control with stable insulin dosing were evident. The median duration of admission was 6 days (range 3–13 days). The median duration of subcutaneous insulin treatment was 5 days (range 3–8 days).

In the univariate regression analysis, covariates with $p <$ 0.2 were selected for the multivariate regression analysis. The following independent variables showed a p value of <0.2 in univariate regression: sex, age, weight, BSA, FFM, DKA status, pH, HbA1C, ketones, vitamin D, T4, and B-lymphocytes.

Table 1 Demographic characteristics of study population. N is number of subjects

	N (percentage) or median (range)
N	70
Sex (M:F)	31:39
DKA (%)	24 (34%)
Age (y)	9.4 (1.3 to 16.7)
Weight (kg)	27 (10.3 to 80)
FFM (kg)	21 (8 to 56)
BMI (kg/m^2)	15.6 (11 to 28.7)
Height (cm)	136 (76.5 to 180)
BSA (m^2)	1 (0.47 to 1.97)
HbA1c on admission (mmol/mol)	103 (59 to 164)
Ketone concentration (mmol/L)	3.5 (0 to 7)
TDD on first day (units)	21 (4.5 to 70)
TDD/kg* on first day (units)	0.7 (0.4 to 1.1)
TDD on last day (units)	27 (5.5 to 124)
TDD/kg* on last day (units)	1.1 (0.3 to 2.2)

*total daily dose per kg of total body weight

In the multiple linear regression, only HbA1C, blood ketone concentration, and weight or FFM were found to be significant predictors for TDD at the $p < 0.05$ level. As the size parameters weight and FFM are strongly correlated, separate multivariate regression analyses were performed using weight and FFM as size variables (Tables 2 and 3).

The results from the multivariate regression analyses are presented below as regression models (Eqs. 1 and 2).

$$TDD = -38 + 1.4 \times WT + 0.17 \times [HbA1C] + 4.3 \times [ketones] \tag{1}$$

$$TDD = -36 + 1.8 \times FFM + 0.15 \times [HbA1C] + 3.7 \times [ketones] \tag{2}$$

Of note, the root mean square error – a measure of model precision – was similar for both models; 10.4 units for the weight-based model and 9.4 units for the FFM-based mode.

Discussion

This study shows that insulin dose requirements in children ($\leq$ 18 years old) with new onset T1DM are influenced by various factors. Assuming minimal changes in dose requirements between the first and last day of admission, the TDD could be calculated more accurately using HbA1C and ketone concentrations on admission in addition to body size. This would potentially improve glycaemic control faster and facilitate earlier hospital discharge.

There is currently no international consensus on the starting dose of insulin in this patient group. This is reflected in a recent survey of medical professionals caring for children with T1DM in Australasia that showed variable insulin starting doses [2]. This variability and the subsequent need for dose adjustments possibly contributes to an increased duration of hospital stay, as patients are stabilised on insulin before discharge.

Previous studies have shown that high HbA1C concentrations in paediatrics with T1DM were associated with insulin resistance [23, 24]. As a corollary, low HbA1C concentrations have been shown to be associated with higher remaining endogenous insulin secretion [25, 26]. The

Table 2 Multivariate linear regression results (with weight as size variable)

Variable	Coefficient	p value	95% CI
Weight	1.4	< 0.001	1.1 to 1.6
HbA1C (mmol/mol)	0.17	0.020	0.03 to 0.30
Ketones (mmol/L)	4.3	< 0.001	2.9 to 5.6
Intercept	−38	< 0.001	−56 to −21

Table 3 Multivariate linear regression results (with FFM as size variable)

Variable	Coefficient	p value	95% CI
FFM	1.8	< 0.001	1.5 to 2.1
HbA1C (mmol/mol)	0.15	0.036	0.01 to 0.28
Ketones (mmol/L)	3.7	< 0.001	2.4 to 4.8
Intercept	−36	< 0.001	−52 to −19

influence of HbA1C on the insulin requirement has also been demonstrated [24, 27].

High ketone concentration is the result of decreased insulin secretion and increased counter-regulatory/stress hormone concentrations such as cortisol and growth hormones [28]. In the current study, ketone concentration on presentation was found to have a significant and independent positive correlation with insulin dose requirements. Although this correlation is expected given the pathology of T1DM, no other studies have quantified the influence of ketone concentration on insulin dose. The work by Weitzel et al. showed a strong association between insulin dose requirements and blood pH, which correlates strongly with ketone concentration [27]. Of note, the dichotomous variable DKA status on presentation was not found to influence insulin TDD. Most patients with DKA received insulin and glucose intravenous infusions prior to the start of subcutaneous insulin and the period of infusions was excluded from the analysis.

The influence of body size on insulin dose requirements was evident in the current study. This has already been established in the literature and the guidelines recommend weight-based dosing. Body weight is relatively easy to measure and correlates well with body metabolism and drug clearance. However, excess fat mass does not contribute to drug clearance hence dose scaling based on body weight in the obese can potentially result in overdosing. Fat-free mass has been developed and used as an alternative to body weight to quantify drug clearance and subsequent dose requirements in obese patients [18]. In this study, FFM performed equally well as a descriptor of body size and a predictor of insulin dose.

Patient age and sex were not found to be significant predictors of insulin dose in this study; once body size, HbA1C, and ketone concentrations were accounted for. Age and sex have been shown to influence insulin resistance and insulin dose requirements in the literature. [23, 27, 29] It is not clear in the current regression analysis whether the lack of statistical significance for age and sex reflects a true lack of covariate effect or a lack of study power to show an effect. Also, the retrospective nature of this study may have limited the amount and quality of data that was collected.

Two dosing algorithms were developed in this study (Eqs. 1 and 2). These equations show the dependence of insulin TDD on body size, HbA1C, and ketone concentrations.

However, for these equations to be used in insulin dose calculation, further model development and evaluation is recommended. This is due to the relatively low study power which is reflected in the relatively wide confidence intervals around the estimated coefficients (Tables 2 and 3). Based on the root mean square error (RMSE) values for these models, a calculated dose can on average be off-target by approximately 10 units. A larger cohort of patients is required to allow for a more precise estimation of these models.

In conclusion, body size, HbA1c, and ketone concentrations have been shown to be significant predictors of insulin TDD in newly diagnosed children with T1DM. Utilising these in initial insulin dose calculations, could potentially decrease the number of days needed to reach a stable dose, and result in improved early glycaemic control. These findings can be used to study a larger cohort of patients in order to quantify the influence of these covariates on dose-requirements.

Compliance with ethical standards

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