AN AUDIT OF CHILDREN WITH TYPE 1 DIABETES MELLITUS PRESENTING TO A TERTIARY INSTITUTION IN JOHANNESBURG, SOUTH AFRICA

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Paediatrics.

Johannesburg, 2021

DECLARATION

I, Meghann Gray, declare that this research report is my original work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university. The submissible format of the research report will be submitted to the Journal of Endocrinology, Metabolism and Diabetes of South Africa, authors guidelines attached in appendix.

Declarations of interest: None.

Dr Meghann Gray **Date: 14 January 2022**

DEDICATION

To all the children and their families living with this condition, and to my family and friends for their unwavering support and encouragement.

PRESENTATIONS ARISING FROM THIS STUDY

1. Oral presentation at 54th SEMDSA Congress, 24 – 28 March 2021.
2. Oral presentation at 1st Virtual SAPA Congress, 13-15 August 2021 and awarded the best oral presentation.

LIST OF ABBREVIATIONS

BAZ	BMI for age z-score
BMI	Body mass index
CHBAH	Chris Hani Baragwanath Academic Hospital
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
FT4	Free Thyroxine 4
GAD	Glutamic acid decarboxylase
HAZ	Height for age z-score
HbA1c	Glycated haemoglobin
IA-2	Islet cell antigen
IAA	Insulin autoantibodies
ICA	Islet cell antibodies
IQR	Interquartile range
ISPAD	International Society for Paediatric and Adolescent Diabetes
SA	South Africa
SD	Standard deviation
TSH	Thyroid stimulating hormone
WAZ	Weight for age z-score
ZnT8	Zinc Transporter

ABSTRACT

Background:

At initial diagnosis, the rate of diabetes ketoacidosis (DKA) varies between countries (15-67%) and may be associated with a lack of awareness of early signs and symptoms.

Objectives:

To describe the demographic, anthropometric, clinical and biochemical characteristics of children presenting with Type 1 diabetes mellitus (DM).

Methods:

A retrospective review of Type 1 DM children's medical records admitted to CHBAH from 01 January 2009 to 31 December 2018 was conducted. This ten-year period was further subdivided into two groups (Group 1: 2009-2013 (n = 75); Group 2: 2014-2018 (n=78)) to assess annual follow-up visit data in Group 1 for five years per patient and to compare data between the Group 1 and 2 time periods. Statistical differences between groups were analyzed by Mann-Whitney U test or Student t-tests, and for between the years of follow-up (Group 1), the paired student t-test was used.

Results:

The total number of newly diagnosed Type 1 DM children was 153. The median age at presentation was 10.5 years (IQR 7.4-12.3), 56% females and 88% black. The mean WAZ and HAZ were -0.8 (SD ± 1.5) and -0.4 (SD ± 1.6) respectively. Sixty-five percent (n = 100) presented in DKA, 56% of those being severe with a higher prevalence of DKA in group 2 compared to group 1 (72% vs 59%; p=0.08). At presentation, the median HbA1c was 12.5% (IQR 11.1-14.3) and C-peptide was 0.2ug/L (IQR 0.1-0.4) (normal range 1.1-1.4). Anti-GAD antibodies were positive in 82% (n=82/101) of the results available. In Group 1, HbA1c increased at year 3 follow up with advancing pubertal status. Despite changing to more intensive insulin therapy, mean HbA1c remained unchanged over the 5 years of follow-up.

Conclusion:

The majority of newly diagnosed children presented in severe DKA, similar to Red Cross War Memorial Children's Hospital (2005-2009), with an increasing prevalence over the ten

years, which could be attributed to the lack of awareness of Type 1 DM in our population. An education campaign is needed to improve community knowledge about diabetes.

ACKNOWLEDGEMENTS

I would firstly like to thank my supervisors, Professor Kebashni Thandrayen and Dr Kiran Parbhoo, for their invaluable input and guidance throughout the process of completing this research report. They were always willing to help me at any time of the day and encouraged me to present my research at two congresses. I shall be eternally grateful to them for their assistance and devotion.

To all the children and their families for allowing their records to be used as part of valuable research into this condition

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INTRODUCTION

Type 1 Diabetes Mellitus (DM) is amongst the most frequent chronic non-infectious diseases in childhood [1]. Type 1 DM is characterized by chronic immune-mediated destruction of the pancreatic beta(β)-cells, which leads to partial or absolute insulin deficiency. This autoimmune destruction of pancreatic β-cells is a T cell-mediated process and probably occurs over months to years before signs and symptoms of diabetes develops [2]. Newly diagnosed Type 1 DM children often present with acute life-threatening complications such as diabetic ketoacidosis (DKA), which could potentially be avoided or prevented with earlier recognition of the signs and symptoms of DM.

An overall 3% worldwide increase in the incidence of Type 1 DM was demonstrated by the Multinational Project for Childhood Diabetes (DIAMOND project) group between 1990 – 1999 and widely varied among different countries and different ethnic populations [3-5]. Type 1 DM is now the third leading chronic disease in children and adolescents [3]. Authors have reported the incidence of Type 1 DM estimated to be in the region of five new cases per 100 000 children per year in the Western Cape, South Africa (SA) between 2005-2009 [1, 6]. There is a paucity of data on the incidence of newly diagnosed Type 1 DM in South Africa. However, two studies have been conducted at tertiary hospitals investigating the characteristics of children with newly diagnosed Type 1 and Type 2 DM. The first study done at Inkosi Albert Luthuli Central Hospital found that 68.9% of children presented in DKA [7], and similarly, the second study at Red Cross War Memorial Hospital showed that 65% of children presented in DKA [8].

Diabetes associated autoantibodies that are serological markers of β-cell autoimmunity include the islet cell antibodies (ICA), insulin autoantibodies (IAA), glutamic acid decarboxylase (GAD65), molecules associated with protein phosphatase IA-2 (Islet Cell Antigen) and IA-2SS and Zinc transporter 8 (ZnT8). The GAD65 and ZnT8A antibodies are also associated with thyroid autoimmunity [9]. These autoantibodies are present in > 90% of children when fasting hyperglycaemia is initially detected [10]. The presence of the diabetes associated autoantibodies are helpful as an important diagnostic tool for Type 1 DM.

C-peptide is a surrogate marker of endogenous insulin secretion. A low C-peptide level implies decreased β-cell function; therefore, when children present in DKA, they are likely to

have low C-peptide levels and higher glucose levels due to this significant β-cell destruction [11].

In a study done at the Barbara Davis Center for Diabetes (BDC) in Colorado, longitudinal glycated haemoglobin (HbA1c) levels up to 15 years after diagnosis showed that the HbA1c levels remained 0.3-1% higher in children who presented in DKA as opposed to those children presenting with mild symptoms [12]. Type 1 DM awareness should be addressed to avoid initial DKA in the first presentation and for better long-term glycaemic control of children [12].

This study investigates the incidence, clinical presentation and complications such as DKA at diagnosis of Type 1 DM and progression of the condition at a tertiary level centre in Johannesburg, South Africa.

METHODS

Study design and population

This is a descriptive study conducted through a retrospective review of medical records of the children admitted with the diagnosis of Type 1 DM to Chris Hani Baragwanath Academic hospital (CHBAH) at their first presentation from 01 January 2009 to 31 December 2018. This ten-year period was further subdivided into two groups (Group 1: 2009-2013 (n = 75); Group 2: 2014-2018 (n=78)). Group 1 was followed up annually for five years, and group 2 was not followed up as the time period was a limiting factor.

Methodology

Children included in the study were between ages 6 months and 14 years and diagnosed with Type 1 DM (as defined by the ISPAD guidelines [10]):

1. Classic symptoms of diabetes or hyperglycaemic crisis, with plasma glucose concentration ≥ 11.1 mmol/L OR
2. Fasting plasma glucose ≥ 7 mmol/L. Fasting is defined as no caloric intake for at least 8 h OR
3. HbA1c ≥ 6.5% [10]

Furthermore, DKA was defined as per ISPAD guidelines as [13]:

4. Hyperglycemia (blood glucose >11 mmol/L)
5. Venous pH <7.3 or serum bicarbonate <15 mmol/L
6. Ketonemia (blood ß-hydroxybutyrate ≥3 mmol/L) or moderate or large ketonuria

The exclusion criteria were: a) the diagnosis of Type 1 DM was determined outside of CHBAH (not newly diagnosed); b) children with Type 2 DM; c) neonatal diabetes, and d) children diagnosed with diabetes caused by other conditions. Data collected at the first presentation included: age, sex, race, anthropometry (using the World Health Organisation criteria [14]), pubertal stage (Tanner staging), DKA at presentation and severity (as defined by ISPAD guidelines in the table below [13]), biochemical characteristics (HbA1c, thyroid antibodies, C-peptide, GAD65 autoantibodies and IAA autoantibodies), family history and employment status. The annual follow up data per patient for Group 1 included: pubertal status, anthropometry, HbA1c, insulin regime (mixed insulin regime with a combination of

short and long-acting insulin or intermediate-acting insulin twice-daily injection with short-acting insulin pre-meals), recurrent DKA admissions and concurrent illnesses. The severity of DKA is categorized by the degree of acidosis [13]:

- Mild: venous pH <7.3 or serum bicarbonate <15 mmol/L
- Moderate: pH <7.2, serum bicarbonate <10 mmol/L
- Severe: pH <7.1, serum bicarbonate <5 mmol/L

Data analysis

The data was captured into a data collection sheet, entered into an excel spreadsheet, and analyzed using Statistica version 13.5 (TIBCO Software Inc, USA).

The incidence of new cases per year of Type 1 DM was calculated using the statistical data on the South African population provided by the Gauteng Department of Health – Health Information Management for years 2011-2018 for the Johannesburg regions G and D.

The statistical analyses are mainly descriptive. Categorical values are reported as numbers and percentages. The continuous variables are reported as means and standard deviations or medians and interquartile ranges (IQRs). Statistical differences between groups were analyzed by Mann-Whitney U test or Student t-tests, and for between the years of follow-up (Group 1), the paired student t-test was used. ANOVA (analyses of covariance) was performed on continuous data such as BMI and HbA1c from the different time points (years) to assess improvement or worsening of these parameters over the 5 years. HbA1c was measured by immunoassays method produced by Roche diagnostics at CHBAH laboratory.

Ethical consideration

Approval for the study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand prior to data retrieval and the analyses of patient records (ref. no. M200259). Study permission was obtained from the CEO of CHBAH and the Head of Department at CHBAH to conduct this research at their institution.

RESULTS

The total incidence of newly diagnosed Type 1 DM from 2009 – 2018 in the Johannesburg population of regions G and D was 3.24 per 100 000 children (Population statistics for 2009 and 2010 not available), as shown in Figure 1. Our incidence rate remained relatively unchanged except for 2017 where it increased to 6.36 per 100 000 children. When patients presenting in 2017 were excluded due to unexplained increased incidence, the total incidence was 2.86 per 100 000 children for years 2011 – 2018 (with 2017 being excluded). The total number of newly diagnosed Type 1 DM children, between 6 months and 14 years, presenting to CHBAH were 153 over the ten years.

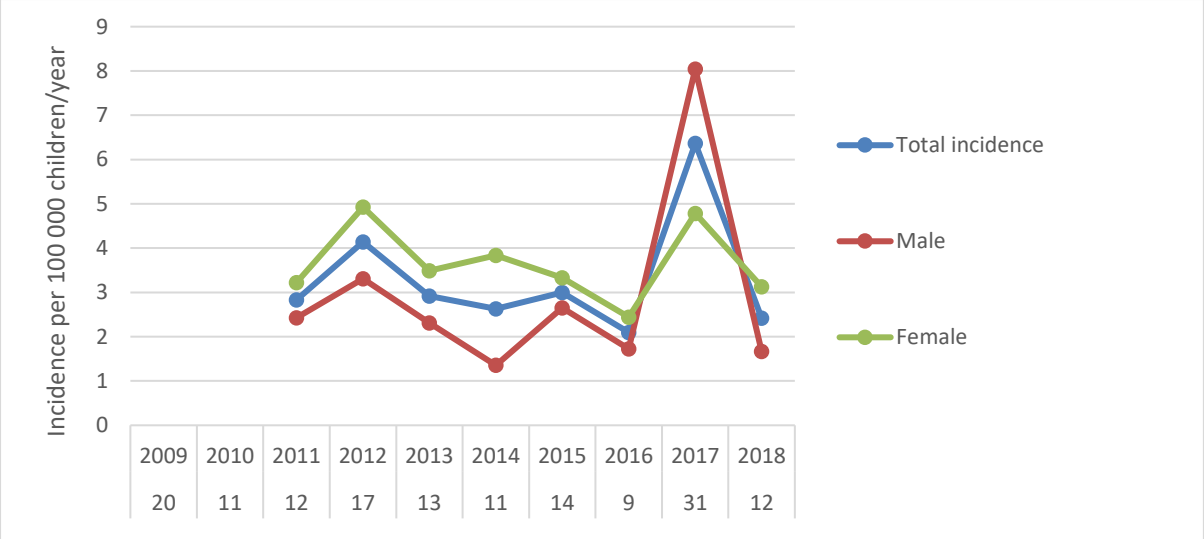

Figure 1: Incidence of newly diagnosed Type 1 Diabetes Mellitus at Chris Hani Baragwanath Academic Hospital

These children were subdivided into two groups (Group 1: 2009-2013 (n = 75); Group 2: 2014-2018 (n = 78)) (Figure 2).

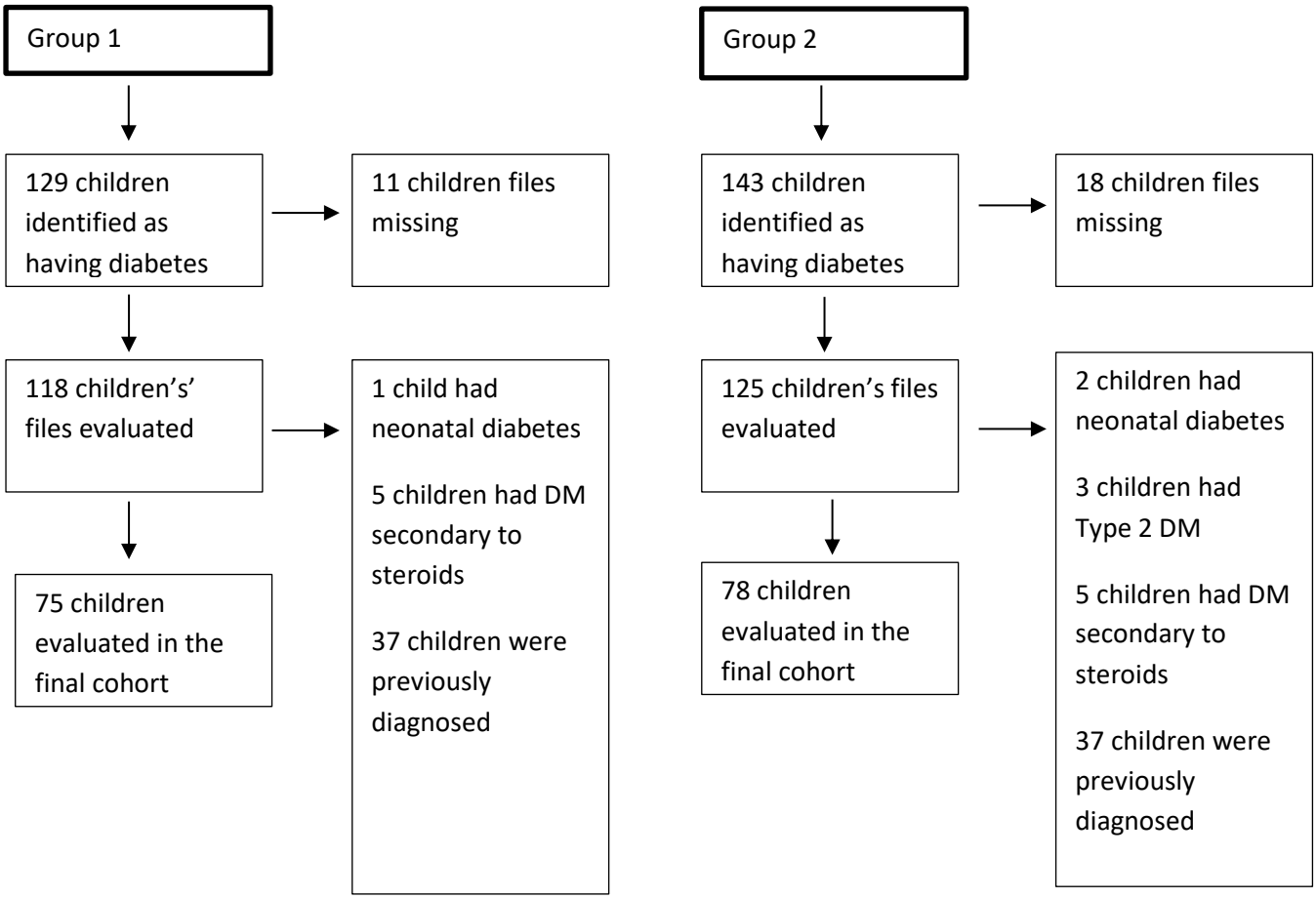

Figure 2: Flow diagram of recruitment of children into the study

Group 1 medical records were reviewed for 5 years, but only 24% (n=18/75) were still followed up at the clinic after 5 years. The outcomes of the children in Group 1 are listed in Table 1 below.

Table 1: Outcome of children in Group 1

Outcome	**N = 75** n (%)
Transferred to Adults	26 (35)
Defaulted	21 (27)
Following up	18 (24)
Transferred to other facilities	8 (11)
Demised	2 (3)

The median age at presentation was 10.5 years (IQR 7.4-12.3), with 57% (n=87/153) who were between ages 10-14 years. Of the 153 children, 56% were female and 88% black. Sixty-five percent (n=100/153) presented in DKA, 56% of those being severe with a higher prevalence of DKA in group 2 compared to group 1 (72% vs 59%; p=0.08). The mean WAZ and HAZ were -0.8 (SD ± 1.5) and -0.4 (SD ± 1.6) respectively. There was a positive family history for DM in a 1st degree relative (41%) with no difference between the two groups (p = 0.60). Fifty-six percent (n=84/153) of children were pre-pubertal at presentation. At presentation, the median HbA1c was 12.5% (IQR 11.1-14.3) and C-peptide was 0.2ug/L (IQR 0.1-0.4) (normal range 1.1-1.4). GAD65 antibodies were positive in 82% (n=82/101) of children that were tested. A greater number of children aged 2-10 years tested positive for GAD65 antibodies, which was significantly higher when compared with children older than 10 years (p = 0.006). Islet cell antibodies were positive in 64% (n=49/77). The majority (82%) of patients between ages 2-10 years were positive for islet cell antibodies (p = 0.006) when compared to ages 0 – 2 years and ages 10 – 14 years. Ten percent (15/153) of children had a comorbid condition at presentation. The significant co-morbidities were that four children were obese, one presented with autoimmune hepatitis and another patient presented with thyroiditis at initial diagnosis of Type 1 DM. Employment status was assessed to determine who the primary caregiver was. When the parents were the primary caregivers, 53% (n = 59/111) of mothers and 27% (24/88) of fathers were unemployed. In the eight cases where the granny was the primary caregiver, all the grannies were unemployed. In 26% of the children, both parents were the primary caregivers.

Table 2: Characteristics of the children at presentation (n=153)

Results			
At Presentation	**N**	**2009 - 2018**	
Demographics			
Age	153	Mean (SD) 9.4 (±3.7)	Median (IQR) 10.5 (7.4 - 12.3)
Sex	153	**n (%)**	
Male		68 (44)	
Female		85 (56)	
		n (%)	
Pubertal	153	67 (44)	
Race	153	**n (%)**	
Black		135 (88)	
Coloured		13 (8)	
Indian		2 (1)	
White		3 (2)	
Anthropometry		Mean (SD)	Median (IQR)
Weight	153	30.7 (±14.6)	29.9 (20.1 - 38.0)
Height	147	132.0 (±23.6)	139.0 (120.0 - 148.0)
BMI	147	16.5 (±4.4)	15.8 (13.4 - 18.1)
Co-morbidities		**n (%)**	
	147	15 (10)	
Presentation			
		n (%)	
DKA	153	100 (65)	
Severity	100	**n (%)**	
Mild		22 (23)	
Moderate		18 (19)	
Severe		56 (58)	
Missing		4 (4)	
Biochemistry		Mean (SD)	Median (IQR)
pH		7.1 (±0.1)	7.1 (6.9 - 7.2)
HC03		7.1 (±4.5)	7.0 (5.1 - 9.4)
BE		-21.1 (±6.4)	-22.1 (-25.5 - -18.0)
Serum Osmolality		312.4 (±21.5)	308.1 (297.0 - 322.0)
Corrected Sodium		139.4 (±8.5)	139.0 (134.0 - 143.9)
HbA1c		12.8 (±3.1)	12.5 (11.1 - 14.3)
C-peptide, thyroid function tests and antibodies			
		Mean (SD)	Median (IQR)
C-peptide	125	-0.8 (±1.6)	-0.8 (-2.1 - 0.2)
FT4	133	-0.8 (±1.5)	-0.8 (-1.9 - 0.2)
TSH	142	-0.4 (±1.7)	-0.3 (-0.7 - 0.0)
Thyroid Ab			
Positive	131	11 (8)	
Anti GAD Ab	97	-0.9 (±1.6)	-0.9 (-2.2 - 0.2)
Positive	101	82 (81)	
Islet cell Ab	77	-0.4 (±1.6)	-0.7 (-1.4 - 0.4)
Positive	77	49 (64)	
GAD / IA2 Ab	86	0.1 (±2.0)	-0.2 (-1.3 - 0.9)
Positive	89	80 (90)	
Insulin regime started			
		Mean (SD)	Median (IQR)
Number of Injections	146	3.3 (±1.1)	4.0 (2.0 - 4.0)

The children in group 1 were shorter than group 2 with a mean HAZ of -1.0 (± 1.3) vs -0.0 (± 1.7); p = <0.01. In group 1, more children presented with severe DKA than in group 2 (66% (n=27/44) vs 53% (n=29/56) respectively; p = 0.04). The children in group 2 were started on

multiple insulin injections (>2) per day at diagnosis compared to group 1 (4.0 injections (IQR 4.0 – 4.0) vs 2.0 (IQR 2.0 – 4.0) respectively; p = 0.00).

The insulin regime changed over the years, which was evident when comparing group 1 and group 2. Fifty-nine percent of children in group 1 were on mixed insulin therapy (combined short and intermediate-acting) or two injections per day, while in group 2, 63% were on separate intermediate twice daily injections and short-acting insulin injections pre-meals, so they received more intensive insulin therapy (p< 0.001) as shown in Table 3.

Table 3: Comparisons between group 1 and group 2 at presentation

	N	At presentation	N	Group 1	N	Group 2	
Demographics							**p-value**
Age Mean (SD) Median (IQR)	153	9.4 (±3.7) 10.5 (7.4 - 12.3)	75	9.9 (±3.4) 10.6 (8.6 - 12.6)	78	8.9 (±3.9) 10.3 (6.7 - 12.0)	p = 0.14
Sex n (%) Male Female	153	68 (44) 85 (56)	75	33 (44) 42 (56)	78	35 (45) 43 (55)	p = 0.91
Pubertal n (%) No Yes	153	84 (56) 67 (44)	75	41 (55) 34 (45)	78	33 (43) 43 (57)	p = 0.81
Race n (%) Black Coloured Indian White	153	135 (88) 13 (9) 2 (1) 3 (2)	75	67 (89) 6 (8) 1 (1) 1 (1)	78	68 (87) 7 (9) 1 (1) 2 (3)	p = 0.95
Anthropometry							
WAZ Mean (SD) Median (IQR)	153	-0.8 (±1.6) -0.8 (-2.1 - 0.2)	75	-1.1 (±1.5) -1.3 (-2.2 - -0.1)	78	-0.5 (±1.6) -0.4 (-1.6 - 0.4)	p = 0.24
HAZ Mean (SD) Median (IQR)	147	-0.4 (±1.6) -0.7 (-1.4 - 0.4)	70	-1.0 (±1.3) -1.2 (-1.7 - -0.3)	77	0.0 (±1.7) -0.2 (-0.9 - 0.7)	p = <0.01
BAZ Mean (SD) Median (IQR)	147	-1.0 (±1.9) -0.9 (-2.2 - 0.5)	70	-1.0 (±1.8) -0.8 (-2.1 - 0.3)	77	-1.0 (±2.0) -0.9 (-2.2 - 0.5)	p = 0.94
Co-morbidities n(%) No Yes	153	132 (90) 15 (10)	72	66 (92) 6 (8)	75	66 (88) 9 (12)	p = 0.46

							p-value
DKA n (%)							
Yes	153	100 (65)	75	44 (59)	78	56 (72)	p = 0.08
No		53 (35)		31 (41)		22 (28)	
Severity n (%)							
Mild	100	22 (22)	44	11 (27)	56	11 (20)	
Moderate		18 (18)		3 (7)		15 (27)	p = 0.04
Severe		56 (56)		27 (66)		29 (53)	
Biochemistry Median (IQR)							
pH	93	7.1 (6,9 - 7,2)	38	7.1 (6.9 - 7.2)	55	7.1 (6.9 - 7.2)	p = 0.55
HC03	90	12.0 (12.0 - 13.0)	37	6.1 (3.5 - 9.1)	53	7.5 (6.0 - 9.7)	p = 0.02
BE	90	11.0 (10.0 - 12.0)	37	-22.0 (-25.5 - -17.0)	53	-22.4 (-25.3 - -18.8)	p = 0.55
Serum Osmolality	79	7.1 (6.9 - 7.2)	31	308.0 (297.6 - 319.0)	48	309.5 (296.9 - 325.5)	p = 0.90
Corrected Sodium	89	7.0 (5.1 - 9.4)	38	137.0 (132.4 - 143.0)	51	139.0 (136.0 - 145.0)	p = 0.08
HbA1C Median (IQR)	139	-22.1 (-25.5 - -18.0)	72	12.4 (11.1 - 14.4)	67	12.6 (11.1 - 14.0)	p = 0.73
C-peptide, thyroid function tests and antibodies							
C-peptide	125	0.2 (0.1 - 0.4)	60	0.2 (0.1 - 0.4)	65	0.2 (0.1 - 0.4)	p = 0.89
TSH	142	2.0 (1.1 - 3.0)	70	1.8 (1.0 - 2.5)	72	2.0 (1.2 - 3.1)	p = 0.41
FT4	133	16.5 (13.2 - 18.3)	66	16.5 (12.8 - 18.6)	67	16.5 (13.2 - 18.2)	p = 0.96
Thyroid antibodies (TPO) Positive	131	11 (8)	63	4 (5)	68	7 (10)	p = 0.42
Anti GAD Ab	97	100.0 (21.0 - 1000.0)	35	100.0 (34.0 - 493.0)	62	74.0 (18.0 - 1312.0)	p = 0.65
Positive	101	82 (81)	40	33 (83)	61	49 (80)	p = 0.79
Islet cell Ab	77	32.0 (6.0 - 254.0)	17	45.0 (10.0 - 286.0)	60	24.0 (6.0 - 251.5)	p = 0.99
Positive	77	49 (64)	17	12 (71)	60	37 (62)	p = 0.50
GAD / IA2 Ab	86	100.0 (21.0 – 254.0)	22	100.0 (44.9 - 100.0)	64	146.0 (19.6 - 320.0)	p = 0.69
Positive	89	80 (90)	23	21 (91)	66	59 (89)	p = 0.8
Insulin regime started							
Number of Injections	146	4.0 (2.0 - 4.0) 3.3 (±1.1)		2.0 (2.0 - 4.0) 2.7 (±1.0)		4.0 (4.0 – 4.0) 3.8 (±1.0)	p = 0.00

Over the 5 year follow up period in group 1, there was a significant increase in WAZ and BAZ at each year 1, 2 and 3 compared to baseline (< p = 0.01), as shown in table 4.

Evaluation of pubertal status in 37 children in group 1 revealed that 24% (n=9) were pubertal in year 1, progressing to 59% (n=22) in year 3. Over the years, the HbA1c remained constant, with only a significant increase in year 3 compared to year 1 (p = 0.04), as shown in table 4.

There was an increasing trend in the prevalence of DKA readmissions over the 5 years. In year 5, 38% of children in group 1 (n=7/18) presented with repeated episodes of DKA, with 5 children presenting with a single DKA episode and 2 with recurrent DKA admissions. Children with recurrent episodes of DKA tended to have lower HbA1c at initial diagnosis than those with a single recurrence of DKA (10.98% vs 13.01%; p=0.03). The reasons for the increase admissions could not be ascertained as this was a retrospective study.

Table 4: Temporal trends and anthropometric data in group 1 over the 5 year follow-up

	5 Year Follow Up					
	Baseline 75	**Year 1 71**	**Year 2 49**	**Year 3 37**	**Year 4 28**	**Year 5 18**
Age						
Mean (SD)	9.9 (±3.4)	10.8 (±3.4)	11.3 (±3.2)	11.6 (±3.3)	12.0 (±3.1)	11.8 (±3.0)
Median (IQR)	10.6 (8.6 - 12.6)	11.5 (9.5 - 13.6)	12.1 (10.5 - 13.7)	12.6 (9.7 - 13.7)	12.8 (10.2 - 14.1)	12.9 (9.3 - 14.2)
Anthropometry						
WAZ						
Mean (SD)	**-1.1 (±1.5)** *	-0.6 (±1.4)	-0.7 (±1.2)	-0.6 (±1.3)	-0.7 (±1.4)	-0.9 (±1.6)
Median (IQR)	**-1.3 (-2.2 - -0.1)**	-0.6 (-1.6 - 0.2)	-0.8 (-1.6 - 0.3)	-0.6 (-1.2 - 0.3)	-0.4 (-1.1 - 0.2)	-0.7 (-1.1 - -0.1)
HAZ						
Mean (SD)	-1.0 (±1.3)	-0.8 (±1.2)	-0.8 (±1.2)	-0.7 (±1.2)	-0.8 (±1.1)	-0.9 (±1.2)
Median (IQR)	-1.2 (-1.7 - -0.3)	-1.0 (-1.5 - -0.1)	-0.9 (-1.7 - 0.1)	-0.5 (-1.4 - 0.2)	-0.9 (-1.4 - 0.2)	-0.6 (-1.5 - 0.1)
BAZ						
Mean (SD)	**-1.0 (±1.8)** *	-0.2 (±1.4)	-0.3 (±1.2)	-0.3 (±1.3)	-0.4 (±1.6)	0.5 (±4.9)
Median (IQR)	**-0.8 (-2.1 - 0.3)**	-0.4 (-1.0 - 0.6)	-0.4 (-1.1 - 0.6)	-0.2 (-1.0 - 0.7)	-0.1 (-1.1 - 0.8)	-0.3 (-1.0 - 0.6)
Pubertal	**n = 75**	**n = 68**	**n = 48**	**n = 37**	**n = 27**	**n = 17**
No	41 (55)	29 (43)	16 (33)	15 (41)	11 (41)	8 (47)
Yes	34 (45)	39 (57)	32 (67)	22 (59)	16 (59)	9 (53)
HbA1c						
Mean (SD)	12.7 (±3.1)	11.8 (±3.7)	12.1 (±3.1)	**12.8 (**±2.2)**	12.4 (±3.1)	13.3 (±2.5)
Median (IQR)	12.4 (11.1 - 14.4)	12.3 (8.0 - 14.0)	13.5 (9.6 - 14.0)	**13.2 (12.2 - 14.0)**	14.0 (11.5 - 14.0)	14.0 (13.0 - 14.0)
Insulin Mean Dose (U/Kg/Day)						
Mean (SD)		0.8 (±0.2)	0.8 (±0.2)	0.8 (±0.2)	0.8 (±0.3)	0.8 (±0.3)
Median (IQR)		0.8 (0.6 - 0.9)	0.8 (0.7 - 0.9)	0.9 (0.7 - 1.0)	0.9 (0.8 - 1.0)	0.8 (0.8 - 1.1)
Number of Injections						
Median (IQR)	2.7 (±1.0)	2.0 (2.0 - 4.0)	2.0 (2.0 - 3.0)	2.0 (2.0 - 4.0)	3.0 (2.0 - 4.0)	4.0 (2.0 - 5.0)
Number of DKA Presentation n (%)						
DKA admissions	44 (59)	32	24	15	6	12
Children presenting with single DKA admission		12 (17)	10 (20)	5 (13)	1 (3)	5 (25)
Children presenting with recurrent DKA admissions		6 (9)	5 (10)	4 (10)	2 (7)	2 (10)
Concurrent illness						
No	66 (92)	51 (75)	40 (82)	29 (78)	25 (93)	15 (83)
Yes	6 (8)	17 (25)	9 (18)	8 (22)	2 (7)	3 (17)

* $p < 0.001$ comparing years 1-3 to baseline
** $p = 0.04$

DISCUSSION

Type 1 DM is the most frequently encountered chronic childhood disease with incidence rates slowly rising globally, with the most marked increase in the very young and in countries experiencing rapid economic growth [4, 15, 16]. The overall incidence rate in Poland, Silesia, increased by 3.8 times from 1989-2012, with the highest annual increase in children between 5 and 9 years of age [17]. There is a paucity of data from low- and middle-income countries, leading to inaccurate estimations of the real burden of disease in those countries.

There is a large variability in the incidence of Type 1 DM in childhood among different populations. This variability could be explained by differences in ethnic background, geographical regions, and the level of industrial development and suboptimal data collection [15]. The incidence of Type 1 DM from our study at CHBAH was 3 new cases per 100 000 children/year (< 14 years of age) but with an increase in 2017 to 6.3 per 100 000 children. There was no difference in the incidence between males and females throughout the years (2011-2018). This incidence in Johannesburg South is lower than the estimated five new cases per 100 000 reported by Robertson in the South African Health review 2006 at Red Cross Children's Hospital Diabetic clinic in the Western Cape [1]. Non referral of children to hospital because of non-recognition of diabetes could potentially account for the lower perceived incidence.

DKA is an acute life-threatening complication of newly diagnosed Type 1 DM and presents in 30 – 40% of children in the USA [12]. Up to 80% of children diagnosed with Type 1 DM worldwide present in DKA, as shown in a systematic literature review conducted by Usher-Smith et al. [18]. A multicentre analysis from 106 paediatric diabetes centres in Germany and Austria reported that 21.1% of newly diagnosed Type 1 DM children were admitted with DKA. The frequency of DKA, however, remained unchanged between 1995 – 2007 but was highest among children <5 years of age (26.5%) [19]. Our study showed that 65% of the children presented with DKA. There was an increase in the prevalence of DKA admissions in group 2 compared to group 1 (72% vs 59%; p=0.08) at presentation, which was marginally significant, showing a trend toward an increase in prevalence over the 10 years. Group 1 presented with more severe DKA presentations than group 2 (p=0.04). The bicarbonate in group 1 was significantly lower than in group 2 (p = 0.02), confirming that group 1 had more severe DKA presentations than group 2. This could possibly be attributed to delayed

presentation to hospital either due to lack of transport or delayed referral from the local clinic. Despite changing to more intensive insulin therapy, more injections per day, the mean HbA1c remained unchanged over the 5 years. In a retrospective cohort study done at Tygerberg Hospital, Western Cape, the number of injections increased from 2.93 between August 2004 and July 2005 to 3.14 from September 2010 to July 2011 [(1)]. There was a decrease in HbA1C levels, but it was difficult to distinguish whether this was due to the increasing the number of insulin injections, proper injection technique utilized or introducing a diabetic nurse educator [(1)].

The SEARCH for diabetes in youth study found that children presenting in DKA had poor long term glycaemic control with higher HbA1c levels at 9.9% vs 8.9% in children presenting without DKA [(20)]. The Better control in Paediatric and Adolescent diabetes: Working to create CEnTers of Reference (SWEET) study is a large multinational consortium of paediatric diabetes clinics worldwide that found HbA1c to be the highest in children presenting in DKA with coma compared to those without coma at diagnosis and at year three following the diagnosis [(21)]. In the SWEET study, it was speculated that year-three HbA1c is more closely related to the level of HbA1c at presentation than the patient's clinical presentation. A high HbA1c at presentation indicates long-standing disease (and lack of recognition of symptoms) prior to admission [(21)].

There has been a trend towards an earlier age distribution in most reports internationally. This was alluded to in the discussion above. The majority of our children diagnosed with Type 1 DM were between ages 10 and 14 years, similar to a study done in Jordan during 1992 – 1996 [(22)]. A similar study to our cohort was conducted at the Jordan University Hospital from January 2012 to December 2016, which showed a peak incidence of diagnosis of Type 1 DM between ages 6 and 8 years [(4)]. The higher median age could be attributed to the lack of awareness of the signs and symptoms of Type 1 DM and, therefore late diagnosis or environmental and socioeconomic factors may be different in SA compared to other countries of higher income levels; attributing to the older age at presentation. A study done in the capital of Mali, Bamako, at Hospital du Mali, found the peak age of onset was 15-16 years of age, with the youngest diagnosed at 13 months [(23)]. A Turkish study done in Diyarbakir showed a peak incidence at a younger age (5-9 years) in girls and not in boys [(15)]. There is a varying peak age of presentation of Type 1 DM, possibly due to varying genetic or environmental factors and socioeconomic status in different countries or ethnic backgrounds. It is vital to diagnose children at a younger age as metabolic tracking could start even before

the diagnosis of Type 1 DM is made. This will only be possible if the awareness about Type 1 DM improves in the community.

At initial presentation, 82% (n=125/153) of our children had a median C-peptide of 0.2ug/L (IQR 0.1-0.4). Most of our children aged 2-10 years had positive antibodies for GAD65 and IA2. In addition, 55% of the GAD65 positive were female. This was also shown in previous studies in Jordan as GAD65 and IA2 antibodies are associated with older age (6-10 years of age) and in females [4]. These autoantibodies are age-dependent, with seroconversion of insulin antibodies occurring earlier than other autoantibodies [4]. These autoantibodies are present in > 90% of children when fasting hyperglycaemia is initially detected [10]. Only 8% (11/131) had positive antithyroid antibodies, compared to a study done in Sweden between May 2005 and October 2009 with 12.3% (299/2433) being positive [24].

Ascertainment of family history is important for appreciating genetic susceptibility, and is essential to study the impact of genetic factors and improve diabetes awareness. Our study reported that 41% of children had a positive family history of DM, either first or second-degree relative. This was lower than that reported by Demirbilek et al., where 61% of their children had a positive family history for Type 1 or Type 2 DM [15].

The challenge of managing Type 1 DM includes a lack of awareness of the disease. Therefore, an awareness campaign is necessary to reduce DKA at presentation for newly diagnosed Type 1 DM. A study done by King et al. at Sydney Children's Hospital and Royal North Shore Hospital showed a 64% reduction in DKA at presentation and a lower blood glucose level at presentation after introducing diabetes education campaigns in schools, childcare centres and doctors' offices [25]. The introduction of a poster public health campaign in Mali showed a rise in incidence from 0.12/100 000 in 2007 to 0.35/100 000 in 2016, with a peak in 2014 (the year after the public education campaign) [23]. The Changing Diabetes in Children (CDiC) is a program working on improving awareness in pan-India through over 20 centres giving details of symptoms, diagnosis, diet, monitoring and management of diabetes as well as newsletters, CMEs, online courses and structured teaching modules for diabetes educators [26]. In addition to the importance of increasing awareness for early recognition or diagnosis of Type 1 DM, so too is it important for the ongoing counselling and support to the children living with Type 1 DM and their families to reduce the rate of DKA readmissions. A similar campaign in South Africa is warranted to address these problems that are encountered.

LIMITATIONS

The limitations of our study are attrition of children with transfer to adult services and loss to follow up. Variations in assays over the years could also affect the results such as HbA1c, autoantibodies and c-peptide levels. HbA1c is a poor indicator of glycaemic control compared to “time in range” which could not be assessed in this retrospective study. A diabetic registry is currently not available to compare the data with this audit.

CONCLUSION

Most of the newly diagnosed Type 1 DM children in our study presented in DKA (65%). Despite the incidence remaining constant over 8 years, the prevalence of DKA presentations in newly diagnosed Type 1 DM remains high and has an upward trend. This could be attributed to the continued lack of awareness of Type 1 DM in this population. An education campaign is needed to improve community knowledge about diabetes.

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APPENDIX A: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Meghann Gray et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M200259

NAME: (Principal Investigator)	Dr Meghann Gray *et al.*
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	An audit of children with Type 1 Diabetes Mellitus presenting to a tertiary institution in Johannesburg, South Africa
DATE CONSIDERED:	28/02/2020
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof K. Thandrayen and Dr K. Parbhoo
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	22/06/2020

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I **agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **February** and will therefore be due in the month of **February** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Meghann Gray (Student number: 2342260) am a student registered for the degree of Masters of Medicine in the academic year 2021.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
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- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
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