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A Description of the Characteristics at Presentation of Children Diagnosed with Diabetes Mellitus from 2005-2009 at Red Cross War Memorial Children's Hospital

For the degree Paediatric MMed

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DECLARATION:

I, *Alida Maria Botes*, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being or is to be submitted for another degree in this or any other university.

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ABSTRACT

Objective: To document the demographics, the pattern of clinical and laboratory characteristics at the time of diagnoses for all the newly diagnosed diabetics younger than 14 years reviewed at the Diabetic clinic at the Red Cross War Memorial Children's Hospital (RCWMH) during 2005-2009.

Method: A retrospective folder review was done of all the newly diagnosed diabetics younger than 14 years old at the age of diagnosis. 225 patients were included for analysis. Patients were grouped according to age into a young group (1 month to < 5 years old), a middle group (5years - < 9 years) and an older group (9years - <14 years). Neonates were excluded as well as children who became diabetic secondary to another condition.

Results: 58% of the patients were female and most of the patients were diagnosed with type 1 diabetes (96%). The median age at diagnosis was 8.5 years with a mean HbA1c of 11, 3%. 68% of the patients were in the normal weight category while 8, 4% of the patients were obese. 148 (65%) of the 225 patients presented in diabetic ketoacidosis (DKA). Only one of the patients classified with type 2 diabetes presented in DKA. 51 (22,67%) of the patients were less than 4 years old at the time of diagnosis. 53% of the Caucasian children were less than 4 years old at diagnosis while most of the children in the black and coloured group were diagnosed after 10 years of age. A seasonal variation was seen especially in the young age group with 66% presenting in autumn or winter months.

Conclusions: Almost a quarter of diabetic children presented before the age of 4 years. A large proportion of patients presented in diabetic ketoacidosis which can be life threatening. Due to lack of information at diagnosis, this could be under reported significantly and calls for increase awareness amongst physicians and parents to recognise symptoms earlier. Prospective studies on childhood diabetes in South Africa are needed as well as a registry for childhood diabetes.

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LIST OF ABBREVIATIONS

BMI: body mass index

DIAMOND: Diabetes Mondale (study group)

DKA: diabetes ketoacidosis

DM: diabetes mellitus

EURODIAB: EUROpe and DIABetes

GAD: glutamic acid decarboxylase

GSH: Groote Schuur Hospital

H0: Classified as eligible to receive free health services

H1: Classification if household income is less than R50 000 per annum

H2: Classification if household income is less than R100 000 per annum

H3: Classification if household income is greater than R100 000 per annum

HbA1c: glycated haemoglobin

HCO3: bicarbonate

HIV: human immunodeficiency virus

ICA: islet cell antibody

ICD: International Statistical Classification of Diseases and Related Health Problems

IQR: interquartile range

IDF: International Diabetes Federation

ISPAD: International Society for Pediatric and Adolescent Diabetes

mmol/L: millimol per litre

mg/dL: milligram per decilitre

MODY: maturity onset diabetes mellitus in the young

N/A: not applicable

OGTT: oral glucose tolerance test

RCWMCH: Red Cross War Memorial Children's Hospital

UCT: University of Cape Town

U/kg: unit per kilogram

U/kg/day: unit per kilogram per day

WHO: World Health Organization

CHAPTER 1

Contents:

1. Introduction and Literature Review

Diabetes Mellitus (DM) is one of the most common chronic diseases in childhood (Majaliwa *et al*, 2008). The incidence of type 1 diabetes mellitus (DM) is rising worldwide, especially amongst children younger than 5 years old (Eurodiab, 2000; Karvonen, 2000). The average worldwide increase in the incidence of Childhood DM according to the DIAMOND study group was 2.8% per annum with a rise in the incidence in Africa, estimated to be 3% per year (Diamond project group, 2006). The World Health Organization (WHO) began the Multinational Project for Childhood Diabetes (Diamond study group) in 1990 to study the epidemiology and incidence of type 1 DM in children. One hundred centres participated in this 10 year period study, collecting data from 57 countries in Asia, Europe, North America, South America, and Africa (Karvonen, 2000). However, for most of the African countries included into the study (Algeria, Tunisia, Sudan and Mauritius), the ascertainment was unsure or very poor. From the EURODIAB registry, the average increase in incidence seen in Europe in the early nineties was 3.4% per annum (Eurodiab Ace Study group, 2000). Alarming information obtained from this registry was the increased rate in incidence of 6.3% seen in the age group 0-4years.

There is paucity of information on both the incidence and epidemiology of childhood diabetes in Africa in general, and South Africa in particular. The International Diabetes Federation reports that 75% of patients with DM are from low- or middle-income countries (IDF Diabetes Atlas 7th edition, 2015). From this report, an estimated 46 400 children under 15 years of age in Africa are living with type 1 DM. This estimation was based on data from Nigeria, Ethiopia, Rwanda, Tanzania, and Zambia. South African data included in the report, were based on adult oral glucose tolerance test results. No data were available on childhood diabetes in South Africa. Some of the reasons postulated for this, is the heavy burden of infectious diseases like HIV infection, tuberculosis and other health issues of a developing world (e.g. malnutrition) (Daneman, 2009).

Diabetic ketoacidosis (DKA) is a life-threatening complication of DM. Although mostly seen in type 1, it is also seen in type 2 DM (Botero, Wolfsdorf, 2005). The frequency and degree of diabetic ketoacidosis varies significantly between countries (Levy-Marchal, Patteron, Green, 2001;

Samuelsson, Padaiga, 2002). If it were possible to increase the awareness of the symptoms and signs of DM, the community members and health workers could identify the symptoms of DM earlier and could potentially, reduce the number of children presenting with this life threatening complication. The prevention program in Italy is proof of the effectiveness of an awareness program in order to decrease DKA at presentation (Vanelli *et al,* 1999).

2. Objectives

The aim of this literature review was twofold. Firstly, to evaluate the literature that is available on childhood diabetes in Africa and secondly, to highlight similarities and differences in the clinical presentation of DM in children at disease onset in Africa and the rest of the world.

3. Search strategy

An electronic literature search was performed using Pubmed® (accessed via University of Cape Town (UCT) Libraries website) and Google Scholar.

The search was done for 'Childhood diabetes' and repeated for 'Childhood diabetes in Africa' and 'Diabetes Ketoacidosis in Africa'. The search was restricted to articles published in the last fourteen years (2000-2013). However, the search for childhood diabetes in Africa was expanded to the last 40 years. All study designs were included. The search was limited to human subjects, English language text, and participant age range between 1 month and 18 years were reviewed for inclusion. All studies identified with this search strategy were reviewed for inclusion. If a study included age groups older than 18 years but information on younger age groups were well defined in it too, it was reviewed for inclusion. Studies that focused on the characteristics at presentation of DM or DKA at presentation were reviewed for inclusion.

Full-text versions of articles meeting the objectives were downloaded via UCT Libraries (http://www.lib.uct.ac.za/). Additional articles were included by cross-referencing the articles included.

Letters, comments, chapters from textbooks, case reports, and lectures were excluded. Guidelines and treatment protocols were also excluded from review of the full text. Studies that focused on DM secondary to other illnesses or medication were not included. Studies that only focused on maturity onset DM in the young (MODY) or type 2 DM were also not included into this review. Studies focusing on the incidence of childhood DM were not included. Most of the studies were retrospective in nature, and employed a wide range of methodologies.

4. Results

The Pubmed search for 'childhood diabetes', yielded 3831 articles. Of these, 163 abstracts meeting the inclusion criteria were selected, of which 63 were suitable, and were fully reviewed. The search for 'diabetes in Africa' only yielded 35 articles, whereas 57 articles were found for the search: 'diabetic ketoacidosis, Africa'. Of those, 6 articles were included.

5. Review and interpretation of the studies

Good quality studies on non-communicable diseases such as childhood DM from Africa are scarce (Gill, Mbaya, Ramaiya, Tesfaye, 2009). This is also evident from the few studies found suitable for review and inclusion into this review (Appendix: Table 1) (Lester, 1986; Elamin *et al*, 1992; Kalk *et al*, 1993; Swai *et al* 1993; Onyiriuka *et al*, 2013; Reddy *et al*, 2013). Lester's research on childhood DM in Ethiopia dates back to 1986 (Lester, 1986). Lester used the World Health Organization's criteria as diagnostic criteria to make the diagnosis of DM (Lester, 1986). Swai *et al*. included all children younger than 19 years if they required insulin to reach glucose control (Swai *et al,* 1993). The remainder of investigators did not state what criteria were used to make the diagnosis of DM (Elamin *et al*, 1992; Kalk *et al*, 1993; Onyiriuka *et al*, 2013; Reddy *et al*, 2013).

Age at diagnosis

Different age categories were included in the different studies reviewed. Lester and Elamin included children younger than 15 years, whereas the study performed in Johannesburg by Kalk *et al*. included

patients up to the age of 35 years (Lester, 1986; Elamin *et al*, 1992; Kalk *et al*, 1993). The average age at diagnosis was 9–10 years in Sudan and Ethiopia (Lester, 1986; Elamin *et al*, 1992). Kalk, Huddle, and Raals' results showed that Caucasians in Johannesburg presented earlier at 12–13 years of age than study participants of African ethnicity, who presented at 22–23 years (Kalk *et al*, 1993). A more recent study from Durban, South Africa, concluded that children presenting in DKA presented at a slightly younger age (7.3 years) compared to the non-DKA group in their study (Reddy *et al*, 2013).

Compared with other countries, South African children seem to present more or less at the same age as children from other parts of the world (Punnose *et al*, 2002; Levy-Marchal, Eurodiab study, 2001; Rosenbauer *et al*, 2002; Galler *et al*, 2010; Ješić *et al*, 2013; Bui *et al*, 2010; De Vries *et al*, 2013; Xin *et al*, 2010; Sameulsson *et al*, 2002; Szypowska *et al*, 2011; Bhatia *et al*, 2004; Lipton *et al*, 2002; Hummel *et al*, 2012). In most of the studies included, children presented mostly after the age of 8 years, except for the studies from North-West Saudi Arabia where children on average presented at the age of 6.7–6.9 years (Al-Magamsi *et al*, 2004; Hamed *et al*, 2005). Quinn and their group, as well as a group from Israel, focused specifically on the younger groups at presentation (Quinn *et al*, 2006; Nimri *et al*, 2007). The average age in the young Israeli group at presentation was 16.2 ± 4.6 months (6– 24 months included), whereas in Boston children less than 6 years were reviewed with an average age at diagnosis of 3.4 ± 1.6 years. It is important to have some knowledge of what the clinical features of DM are in other ethnic groups as South Africa comprises many different population groups from all over the world.

Gender differences

In the African studies, a female preponderance was seen. It was only the Tanzanian group that had a male preponderance at presentation (Swai *et al*, 1993). In Europe and the United states, a male preponderance was mostly seen (Rosenbauer *et al,* 2002; Galler *et al,* 2010; Ješić e*t al,* 2013; Lipton *et al,* 2002; Quinn *et al,* 2006; Hummel *et al,* 2012). In the Arab studies and the study from Kuwait, as in most African studies a female preponderance was seen (Punnose *et al,* 2002; Al-Magamsi *et al,* 2004; Hamed, *et al,* 2005; Abdoul-Rasoul *et al,* 2010).

Diabetic ketoacidosis at initial presentation

DKA is a life threatening complication of DM. Cerebral injury is the main cause of death of this complication characterised by hyperglycaemia, acidosis, and ketonuria and or ketonaemia (Wolfsdorf *et al,* 2014). DKA can also influence memory function comparable to the effect of mild cerebral hypoxia (Ghetti *et al,* 2010). Diagnostic criteria used to define DKA and to divide it into mild, moderate, and severe DKA, differed between the studies. A summary of the different criteria used by the authors included in Appendix A. Onyiriuka's group used the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines to diagnose DKA (Onyiriuka *et al,* 2013). Using these guidelines, they reported that 77.1% of children and adolescents in their Nigerian study, presented in DKA (Onyiriuka *et al,* 2013). The study from Durban (South Africa) showed similar results, with almost 70% of children presenting in DKA (Reddy *et al,* 2013). The majority of the children in this study were black Africans. Ethnicity did not have an impact on the characteristics of the patients at presentation in their study. All the children aged 5–9 years in their study presented in DKA. The authors did not comment on what criteria were used to make the diagnosis of DKA. In contrast with what was found in the Nigerian study, the group who presented in DKA had a shorter duration of symptoms before they presented (Onyiriuka *et al,* 2013; Reddy *et al,* 2013).

In an older study conducted by Lester in Ethiopia in 1986, seven of the 80 patients presented in DKA. In that study, DKA was diagnosed on clinical grounds: the presence of hyperglycaemia, dehydration, acidosis, and ketonuria in an unconscious patient. Of the children included, 12% had died 9 years post-diagnosis: Four secondary to DKA and four secondary to renal complications. A review by Murunga and Owira states that poor healthcare infrastructure, poverty, ignorance, and the burden of infectious diseases might be blamed for the prevalence of DKA in Sub-Saharan children (Murunga *et al,* 2013). According to the DERI study group less than one percent of Sub-Saharan children with DM will survive more than six years post-diagnosis (Makame, 1992). These were the estimates made twenty years ago. It raises the question: What is the current mortality and morbidity of childhood DM in Sub-Saharan Africa?

The proportion of children presenting in DKA in Lithuania compared with Sweden, was higher (Sadauskaitė-Kuehne *et al,* 2002), yet the incidence of DM in Lithuania is a third of that in Sweden. The children in Lithuania presented more acidotic and with higher glycated haemoglobin (HbA1c) levels compared with their Swedish counterparts. The incidence of DM in Africa is amongst the lowest in the world, and is mostly estimated numbers (IDF Atlas 2015). Misdiagnosis significantly increased the chances of DKA at presentation in another study from Scandinavia (high incidence area), which showed a prevalence of 26% of DKA at diagnosis (Szypowska *et al,* 2011). Children presenting with DM in a Canadian study had at least one medical encounter in the week prior to the diagnosis (Bui *et al,* 2010). An increased risk of delay in diagnosis was seen in older female patients in a study from Germany (Rosenbauer *et al,* 2002). In contrast, there was, interestingly, no difference in the risk of DKA at presentation if the diagnosis was initially missed in South Africa (Reddy *et al,* 2013).

Children younger than 2 years are more at risk of presenting in DKA, comprising 71% of those presenting in DKA in Warsaw (Szypowska *et al,* 2011). The studies from Israel and Boston (USA) echoed this phenomenon with 83% of children younger than 2 years at diagnosis in Israel presenting in DKA (Nimri *et al,* 2007, Quinn *et al,* 2006; De Vries *et al,* 2013). Younger children were symptomatic for a shorter period of time before presentation, had significantly lower HbA1c levels and were more symptomatic; 36% presented with impaired consciousness (Nimri *et al,* 2007; Rosenbauer *et al,* 2002).

Rosenbauer, Icks and Giani performed a population-based study in Germany focusing on 'predictors' of severe DKA at onset of type 1 DM (Rosenbauer *et al,* 2002). Severe ketoacidosis, defined as a pH $\leq$ 7.2, was present in 16% of the children with severe DKA. Severe ketoacidosis was present more frequently in children under 4–years of age, and those of lower social status (assessed as highest parental school education). A sub-sample of patients was reviewed according to the presence of a family history of DM, revealing a family history in 35%. A family history of DM was associated with a less severe onset of disease.

None of the studies from Africa included HbA1c measurements in their laboratory tests. This is likely being due to the unavailability or the cost involved in doing the test. Glycated haemoglobin reflects the mean glucose concentration over the preceding 8–12 weeks (Mayo Clinic laboratories, www.mayomedicallaboratories.com). Mean HbA1c values were higher in the DKA group compared to the non DKA group (De Vries *et al,* 2013; Quinn *et al,* 2006). In the study from Boston the DKA group had a mean HbA1c value of 10.8 ± 2.4%, whereas the DKA group from Tel Aviv had a mean value of 12.1 ± 2.8% (Quinn *et al,* 2006; De Vries *et al,* 2013). The difference in values found between the two studies might be explained by the fact that the study in Boston only included children less than 6 years old. The study by Nimri, Phillip and Shalitin compared older children to those less than two years old (Nimri *et al*, 2007). They demonstrated that younger children present with lower HbA1c values compared to the older group they investigated, implying a shorter duration of illness or some residual beta-cell activity.

6. Conclusion

A high percentage of children in Africa will present in DKA. Information from other countries highlights several factors which should be kept in mind. Younger children present more acutely, with a shorter period of preceding symptoms. Lower socio-economic status increases the risk of DKA at presentation, while a family history of DM might reduce the severity of disease at presentation.

The paucity on data from Africa and South Africa makes it difficult to plan for the future. There is a need for further research to evaluate the characteristics of DM in South African children. In addition, follow up studies are required to evaluate the long term complications of DM in South African children. More information is required, specifically on the incidence of DM. A registry for childhood DM is urgently needed in order to establish the incidence of the disease.

Public awareness of the symptoms of DM in children needs to be improved in order to decrease the prevalence of DKA at presentation.

Table 1: Studies included for review.

First Author	Country/ City	Diagnostic criteria	Age at diagnosis	Gender predominance	DKA [1] (%)	DKA criteria	HbA1c [2] (%)	Antibody
Arabic countries:								
Punnose (2002) Retrospective	Al-Ain City (United Arab Emirates)	WHO	9.2±4.1 years *All < 18 yrs included*	Female	80	Gluc>13.88 mmol/L + HCO3< 15mmol/L +ketonuria	N/A	N/A
Al-Magamsi (2004) Retrospective	Al-Madina region (North West Saudi-Arabia)	WHO[3]	6.9 years (mean) *All < 15 yrs included*	Female	55.2	Gluc > 14 mmol/L + pH <7.3 or HCO3 <15 mmol/L + ketonuria	N/A	N/A
Hamed (2005) Retrospective	Al-Madina region (North West Saudi-Arabia)	WHO	6.7 years (mean) (Patients in DKA) *All < 15 yrs included*	Female (Patients in DKA)	55.3	Gluc > 14 mmol/L + pH <7.3 or HCO3 <15 mmol/L + ketonuria	N/A	N/A
European countries:								
Levy-Marchal (2001) Prospective	Eurodiab study centres[5]	Not stated	8.5±3.89 *All <15 yrs included*	Unknown	42	pH<7.3	N/A	N/A
Rosenbauer (2002) Prospective	North Rhine-Westphalian Region (Germany)	Not stated	Age categories used 41.2% in 10-14yrs *All<15 yrs included*	Male	53.8	pH<7.35	187%[6]	N/A
Galler (2010) Retrospective	Saxony (Germany)	ISPAD[4]	8.6±4.0 years *All <15 yrs included*	Male	27.1	pH<7.3	11.2±2.6	N/A
Ješić (2013) Retrospective	Belgrade (Serbia)	Not stated	9.5±4.0 *All<18 yrs included*	Male	32.9	pH<7.3, blood glucose>11mmol/l, HCO3<15mmol/l and ketonuria	11.6±2.3	N/A

First Author	Country/ City	Diagnostic criteria	Age at diagnosis	Gender predominance	DKA [1] (%)	DKA criteria	HbA1c [2] (%)	Antibody
Scandinavia:								
Samuelsson (2002) Prospective	South-East Sweden, Luthuania	WHO	8.5 (Sweden) vs 9.3(Lithuania) *All <15 yrs included*	Unknown	14.5 (Sweden) vs.34.6	pH<7.3+hyperglycaemia+ketonuria	9.7±2.5 (Sweden) 11.5±2.3	N/A
Szypowska (2011) Retrospective	Warsaw, Mazowieckie district (Poland)	Not stated	8.9±4.6 yrs *All <18 yrs included*	Female	26	pH<7.3 +blood glucose >11mmol/L	11.3±2.2	N/A
India:								
Bhatia (2004) Retrospective	North India	If insulin required	10.6±4.5 *All <18 yrs included*	Not stated	56	Ketonuria +symptoms of acidosis	N/A	N/A
United States:								
Lipton (2002) Retrospective	Chicago	Not stated	10.5 *0-17 yrs included*	Male	73.8	Not stated	N/A	N/A
Quinn (2006) Retrospective	Boston	Based on symptoms	3.4±1.6 *0-6 yrs included*	Male	43.7	Glucose>16.6 mmol/L, pH<7.3, HCO3 <15.5mmol/L	10.8±2.4 (DKA) 9.6±2.0 (Non-DKA)	N/A
Hummel (2012) Retrospective	Colorado	Antibody testing or diagnosis made by physician	<5 21.7% 5-9 33.02% 10-14 33.21% 15-20 12.11% *All <20yrs included*	Male	N/A	N/A	11.1±2.5	GAD[7] 47.96% ICA [8] 56.42%

First Author	Country/ City	Diagnostic criteria	Age at diagnosis	Gender predominance	DKA [1] (%)	DKA criteria	HbA1c [2] (%)	Antibody
Canada:								
Bui (2010) Retrospective	Ontario	ICD-9 coding	9.9±4.7 *All < 18 yrs included*	Male	15-21.9	ICD-9 coding	N/A	N/A
Middle-East:								
Nimri (2007) Retrospective	Israel	Based on symptoms or antibodies	16.2±4.6 months 10.28±3.01 yrs *6 months-16 yrs included*	Male	83 (<2yrs) 40 (5-16yrs)	Not stated	11.61±3.47 (Less than 2 yrs) 13.75±3.45 (older group)	56 % (<2 yrs) 75% (5-16yrs)
Abdoul-Rasoul (2010) Retrospective	Kuwait	ISPAD	Age groups: 0-4= 20.5% 5-8= 50.5% 9-12=29% *All < 12yrs old*	Female	37.7	ISPAD	N/A	N/A
De Vries (2013) Retrospective	Tel Aviv Israel	Not stated	9.2±4.7 (DKA group) 10.4±4.7(Non DKA group) *All < 20 yrs included*	Unknown	33.7	pH<7.3, HCO3<15 mmol/L	12.1±2.8 (DKA group) 11.3±2.9 (Non DKA group)	N/A
East Asia:								
Xin (2010) Retrospective	Shenyang (North-East China)	Expert committee criteria	8.3±4.0 *All < 14 yrs included*	Female	41.9	Glucose>14mmol/L + pH<7.3 or HCO3<15mmol/L and ketonuria	12.7±2.5	GAD 53% ICA 10% IAA 35% IA-2 41%

First Author	Country/ City	Diagnostic criteria	Age at diagnosis	Gender predominance	DKA [1] (%)	DKA criteria	HbA1c [2] (%)	Antibody
Africa:								
Lester (1986) Retrospective	Adis Abeba (Ethiopia)	WHO	10.1 *All <15yrs included*	Female	9	Hyperglycaemia, dehydration, ketonuria.	N/A	ICA 3/6 positive
Elamin (1992) Prospective	Khartoum (Sudan)	Not stated	9.3 (Boys) 9.1 (Girls) *All < 15 yrs included*	Female	N/A	N/A	N/A	N/A
Kalk (1993) Retrospective	Baragwanath, Johannesburg (South Africa)	Not stated	22 (African group) 12-13 (Caucasian) *All < 35 yrs included*	Female	N/A	N/A	N/A	N/A
Swai (1993) Prospective	Dar es Salaam (Tanzania)	All who required insulin	58% in 15-19 age group *All <19 yrs included*	Male	N/A	N/A	N/A	N/A
Onyiriuka (2013) Retrospective	Benin City (Nigeria)	Not stated	12.7±2.6	Female	77.1	ISPAD guidelines	N/A	N/A
Reddy (2013) Retrospective	Durban (South Africa)	Not stated	7.3 (DKA group) 8.5 (Non DKA group) *All <16 yrs included*	Female	69.8	Not stated	N/A	N/A

1-Diabetic ketoacidosis, 2- Glycated haemoglobin, 3- World Health Organization, 4- International Society for Paediatric and Adolescent Diabetes, 5- Austria, Hungary, Iceland, France, Netherlands, Italy, Israel, Lithuania, Latvia, Estonia, Luxembourg, Germany, Portugal, Bulgaria, Romania, United Kingdom, Poland, Slovenia, Slovak Republik, 6- Percentage relative to local upper limit (but not stated).

Shaded columns = studies focusing on DKA at presentation

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CHAPTER 2

Contents:

1. Subjects and Methods

A retrospective folder review was performed at Red Cross War Memorial Children's Hospital (RCWMCH) Diabetic clinic. RCWMCH is a tertiary institution with a bed capacity of 290. Tertiary level patients as well as referrals from within the catchment area are evaluated. RCWMCH drains patients from the Southern suburbs of Cape Town as well as the Cape Flats including Athlone, Mitchell's Plain, Gugulethu, Hanover Park, Heideveld, Nyanga and parts of Khayelitsha. The Diabetes clinic is situated at RCWMCH and the admission ward is at Groote Schuur Hospital located 4 km away.

The study stretched over a 5-year period, from 1 January 2005 until 31 December 2009. All the children less than 14 years old who presented for the first time with either type 1 or type 2 DM (according to the clinician's classification) at RCWMCH were included. Patients who were referred from private institutions within one month after the diagnosis was made, were also included. The diagnosis was based on clinical symptoms and according to the International Society for Paediatric and Adolescent Diabetes (ISPAD) 2009 guidelines (Appendix A). Patients diagnosed within the neonatal period or who developed DM secondary to medication or to any other secondary causes were excluded from the study.

The patients were grouped according to their ages at diagnosis into a young group', 'middle group' and 'older group', aged < 5 years, 5–9 years and 10–14 years, respectively. The date of diagnosis was recorded as the day when insulin or any other glucose lowering medication was started. The month of diagnosis was also noted in order to describe seasonal variation.

Information gathered from the clinical notes included: the age at diagnosis, gender, source of the referral, socio- economic classification and ethnicity of the patient. Ethnicity and socio-economic classification were included according to the classification on admission. This classification is categorized according to self-reported information provided by the caregiver. A family history of diabetes up to second degree family members was included.

Furthermore, it was included whether the patient presented in diabetic ketoacidosis (DKA) or not. DKA was diagnosed if the ISPAD biochemical criteria (see Appendix A) were met or if it was stated in the referral letter for patients who were already stabilized (especially for those patients referred from the private sector). Body mass indexes (BMI) were calculated for the children older than 2 years of age. For those less than 2 years of age, weight -for -length Z scores were used. The BMI was calculated by using the discharge weight or the last weight recorded in the folder closest to one month after diagnosis was made and the patient was stabilized on treatment. The daily insulin requirement needed for glucose control at discharge was recorded in unit per kilogram per day (U/kg/day).

Biochemical information reviewed included the glycosylated haemoglobin (HbA1c) and antibody test results. The HbA1c is routinely measured on all patients reviewed at the clinic and is performed on a finger prick whole blood sample. (Appendix B for test information). Glutamic acid decarboxylase antibodies (GAD) and islet cell antibody (ICA) results were included if available.

Ethics approval for the study was obtained from the Human Research Ethics committee of the University of Cape Town.

2. Statistical analysis:

The data were collected on a data sheet and then entered into the Epidata 3.1 Program. STATA®/IC 11.1 for Windows Data Analysis and Statistical Software (StataCorp LP, 4905 Lakeway Drive, College Station, TX 77845, USA) was used for the analysis. The Shapiro Wilk test was performed to test for normality. Normally distributed data is described using means and standard deviations and skewed data using medians with interquartile range (IQR). The Pearson chi-squared or Fisher's exact tests were used where appropriate.

CHAPTER 3

Contents

1. Results

A total of 239 newly diagnosed diabetic patients who met the requirements for the study, were identified in the 5-year period. Of those, 14 were ineligible for the study. Eleven patients were excluded on the basis that they developed diabetes secondary to medication usage or due to surgery. Three patients were excluded due to incomplete hospital records (Figure 1).

The 225 eligible patients comprised the study cohort. 58% of the participants were female (Table 1). The median age at diagnosis was 8.5 years for both gender groups with an interquartile range of 5.9-11.5 years for the females and 5.2-11.6 years for the male group. A fifth (22.7%) of the children were younger than 4 years old at the time of diagnosis (young group); 34% were between 5-10 years of age (middle group) and 43. 6% were between 10-14 years old (older group). The youngest child in the cohort was diagnosed at 7 months of age. There was no significant statistical difference in the gender distribution within the three age groups (p=0.8).

Only nine patients in the cohort were diagnosed with type 2 DM. All of the children with type 2 DM were older than 7 years with the median age at diagnosis of 11.6 years. The remainder was classified as having type 1DM with the median age at onset of 8.4 years. None of the children fitted the classification for Maturity onset diabetes of the young (MODY).

In the younger age group, almost half of the children were of Caucasian ethnicity. The middle and older groups were predominantly children of mixed race (Figure 2). However,14. 6% of the children were not classified into an ethnicity group due to the lack of information. There was no significant annual increase in the number of children diagnosed during the study period. Within the different age groups, no significant increase in number of newly diagnosed patients was either observed (Table 2).

A large proportion of children were referred from the private sector. 42% were classified as private patients (on a medical aid) or from a household with a reasonable income of more than R10 000 per month. The remaining children were either from low income households or were seen for free.

A seasonal variation was demonstrated and was especially appreciated in the young age group with 43% of these children presenting in autumn. The 5-9yr old group presented mainly during spring and winter and the older group during winter.

Overall 65% of the children presented with DKA. For 13% of the patients no data on DKA at presentation was available from neither the clinical notes nor the laboratory archives. All the patients who presented in DKA except for one were type 1 diabetics. The patient classified as a type 2 diabetic and presented in DKA was a 13 year-old girl. Almost 70% of the children in the middle and older age groups presented in DKA and also more than half of the children in the young group (Table 3). 67% of the African children and 69% of the mixed race patients presented in DKA at diagnosis. 100 of the children who presented in DKA had a family member with diabetes. A positive family history was present in 68% of the cases included in the cohort. The family members were mostly known to have type 2 DM. For 10% of the patients a family history was not available.

Most of the children (70%) were of normal BMI or weight. 20% were either overweight or obese. Most of these were in the older age group. 11 of the children less than 4 years old were overweight or obese. All the children classified as type 2 diabetics were overweight or obese with most of the type 1 diabetics in the normal weight category (Table 4).

The median HbA1c at diagnosis was 9.5% for the young group, 11.2% in the middle group and 12.2% in the older group (Figure 3). The HbA1c at diagnosis was slightly higher in the type 1 DM group with a mean value of 11.3% versus 10.5% for the type 2 patients. The median HbA1c in Caucasian children was slightly lower than in the other ethnicity groups (Figure 4)

Half of the patients had no antibody testing done or the results were unknown. Of those tested, 33% tested positive for ICA, 59% positive for GAD and 43% tested positive for both antibodies. Only 5 of the children classified as type 2 diabetes had antibody testing. Two tested positive for GAD antibodies and one patient tested positive for ICA (Table 5).

The daily insulin usage at diagnosis in units/kg (U/kg) ranged from 0.2U/kg to 1.6U/kg with a median of 0.75U/kg. However, 62% of children in the older group needed more than 0.6U/kg/day in order to be stabilized prior to discharge with 7% requiring more than 1.0U/kg/day.

Table 1. Demographic details of children newly diagnosed with diabetics

Variable	Total	Age group			p value
		1 month-4 years (young group)	5-9 years (middle group)	10-14years (older group)	
n (%)	225 (100%)	51 (22.7%)	76 (33.8%)	98 (43.5%)	
Gender:					
Male	94 (41.8%)	23 (45.1%)	32 (42.1%)	39 (39.8%)	0.82
Female	131 (58.2%)	28 (54.9%)	44 (57.9%)	59 (60.2%)	
Total	225 (100 %)	51 (100 %)	76 (100 %)	98 (100 %)	
Ethnicity:					
African	34 (15.1%)	3 (5.9%)	8 (10.5%)	23 (23.5%)	<0.001
White	47 (20.9%)	25 (49.0%)	10 (13.2%)	12 (12.2%)	
Mixed	111 (49.3%)	15 (29.4%)	44 (57.9%)	52 (53.1%)	
Unknown	33 (14.7%)	8 (15.7%)	14 (18.4%)	11 (11.2%)	
Total	225 (100 %)	51 (100 %)	76 (100 %)	98 (100 %)	
Socio-economic:					
Low income	106 (47.1%)	19 (37.2%)	37 (48.7%)	50 (51.0%)	0.067
Middle	22 (9.8%)	1 (2.0%)	10 (13.2%)	11 (11.2%)	
High income	95 (42.2%)	30 (58.8%)	28 (36.8%)	37 (37.8%)	
Unknown	2 (0.9%)	1 (2.0%)	1 (1.3%)	0 (0.0 %)	
Total	225 (100 %)	51 (100 %)	76 (100 %)	98 (100 %)	

Table 2. Age groups as diagnosed year for year

Year of diagnosis	**Age group**			**Total**
	1 month-4 years (young group)	5-9 years (middle group)	10-14years (older group)	
n (%)	51 (22.7%)	76 (33.8%)	98 (43.5%)	225 (100%)
2005	7	15	24	46
2006	11	16	20	47
2007	16	10	18	44
2008	6	24	14	44
2009	11	11	22	44

Table 3. DKA at diagnosis:

Variables	DKA at diagnosis			Total
	No	Yes	Unknown	
Socio-economic status:				
H0	1	6	1	8
H1	22	**73**	3	98
H2	4	16	2	22
H3	3	13	5	21
Private	17	39	18	74
Unknown	0	1	1	2
Total	47	148	30	225
Ethnicity:				
African	8	23	3	34
White	10	23	14	47
Coloured	26	**77**	8	111
Other or unclassified	3	25	5	33
Total	47	148	30	225
Family history:				
No	11	33	3	47
Yes	33	**100**	21	154
Unknown	3	15	6	24
Total	47	148	30	225
Age at diagnosis:				
Young	11	**29**	11	51
Middle	11	**52**	13	76
Old	25	**67**	6	98
Total	47	148	30	225
Season at diagnosis:				
Spring	7	30	8	45
Summer	13	29	9	51
Autumn	13	36	9	58
Winter	14	53	4	71
Total	47	148	30	225

Table 4. BMI and type of DM

Type of DM	BMI category					Total
	Normal	Overweight	Obese	Moderate wasting	Severe wasting	
Type 1	155 (75.24)	29 (14.08)	12 (5.83)	5 (2.43)	5 (2.43)	206 (100)
Type 2	0 (0)	2 (22.2)	7 (77.8)	0 (0)	0 (0)	9 (100)
Total	155 (72.09)	31 (14.42)	19 (8.84)	5 (2.33)	5 (2.33)	215 (100)

Data are presented as n (%)

Table 5. Antibody test results *vs* type of diabetes

Type of DM	ICA antibody			Anti-GAD antibody		
	Negative	Positive	Unknown	Negative	Positive	Unknown
Type 1	64	35	117	38	62	116
Type 2	7	1	1	6	2	1
Total	71	36	118	44	64	117

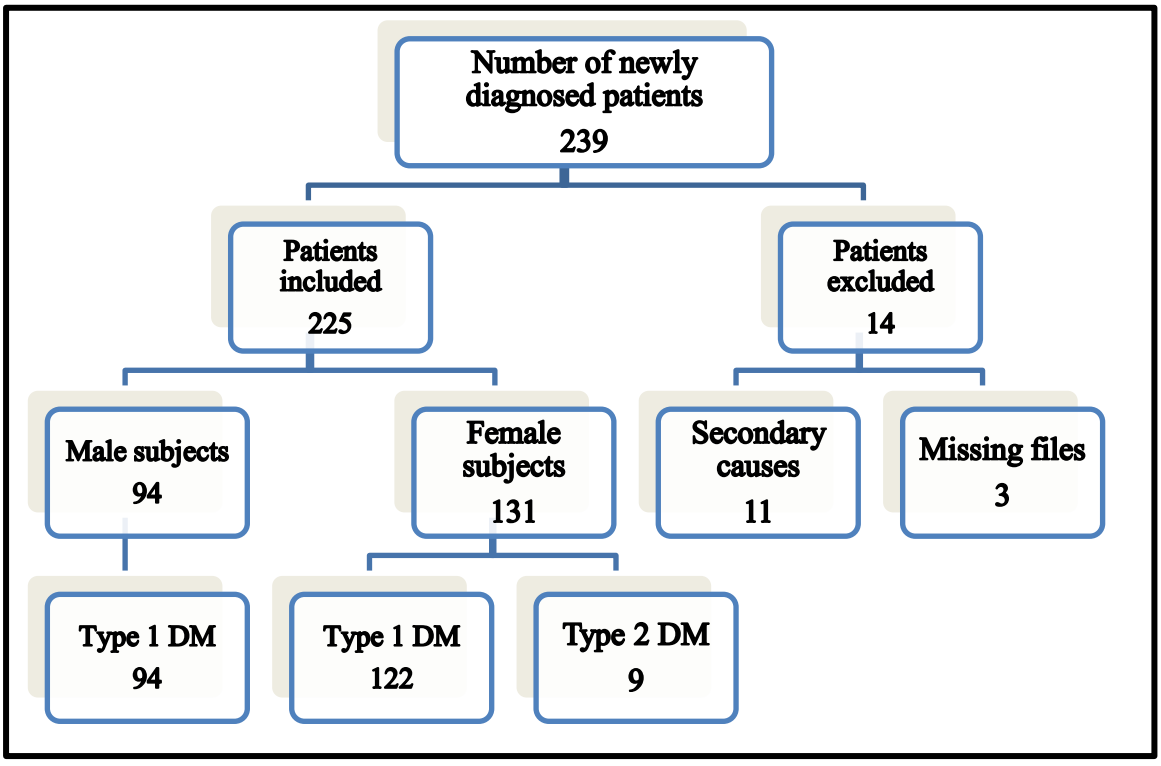

Figure 1. Selection process of patients for cohort

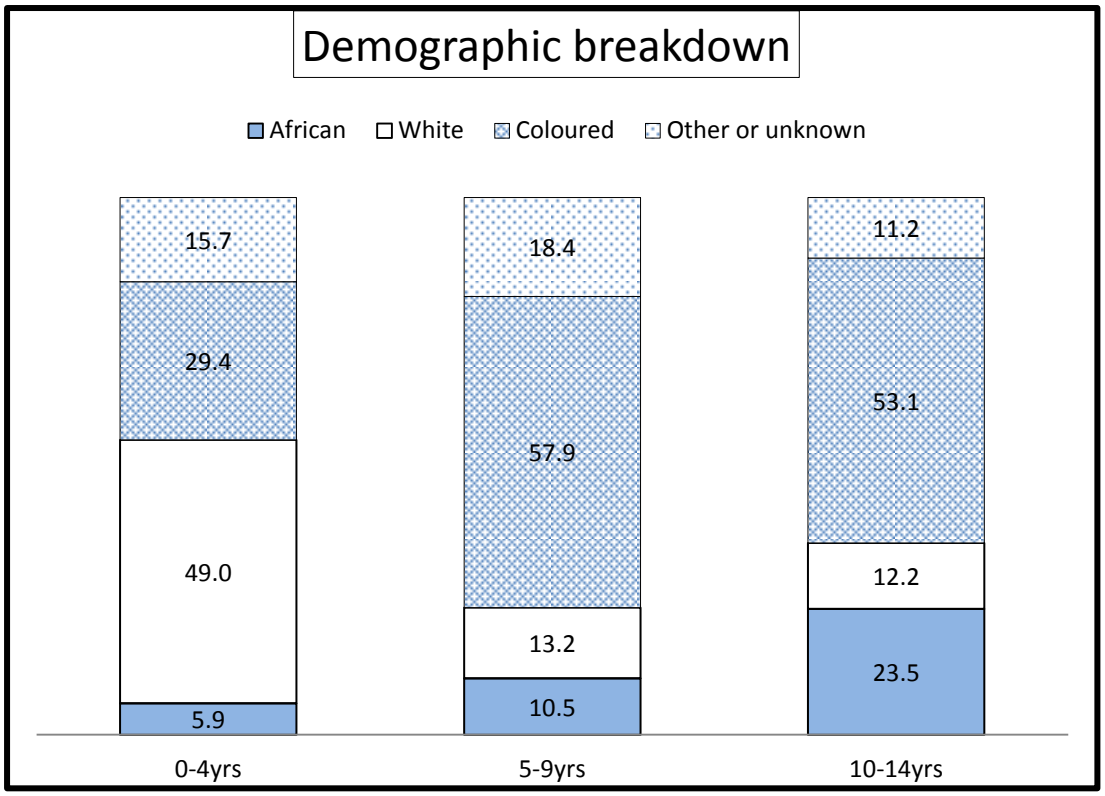

Figure 2: Ethnicity according to the different age groups

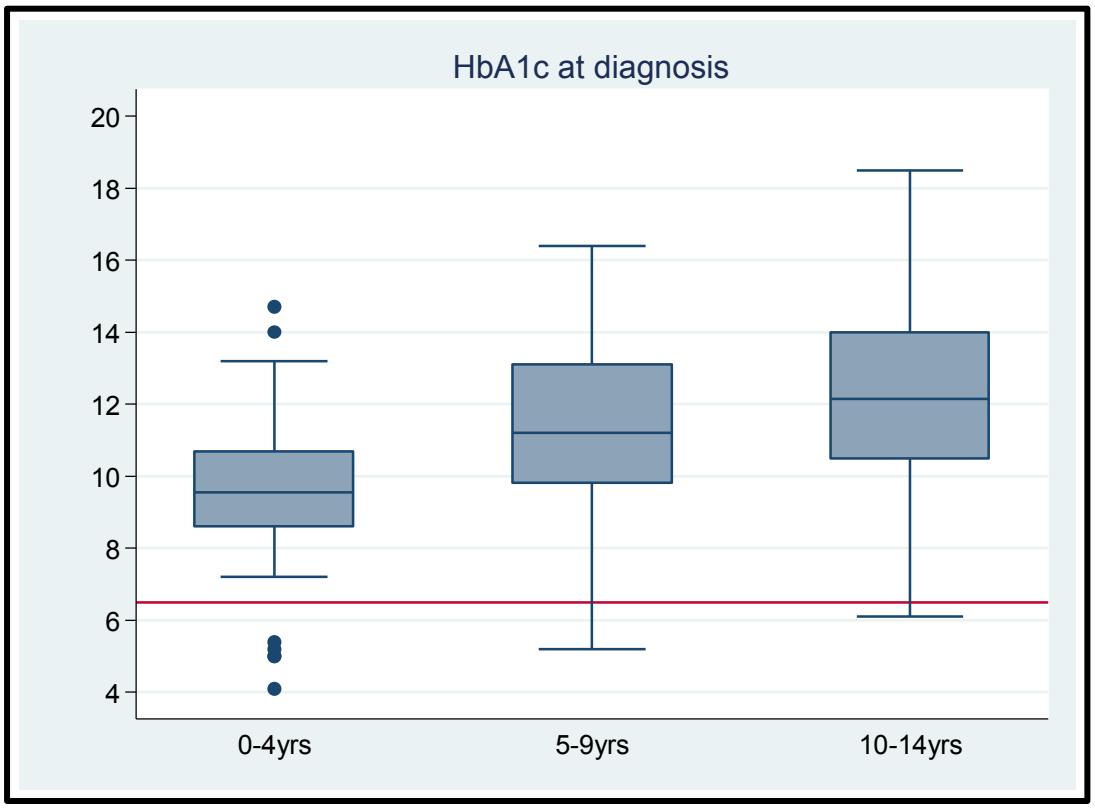

Figure 3: HbA1c at diagnosis according to age group.

Hba1c values on y-axis expressed as %. The red line indicates the HbA1c value accepted as normal or non-diabetic.

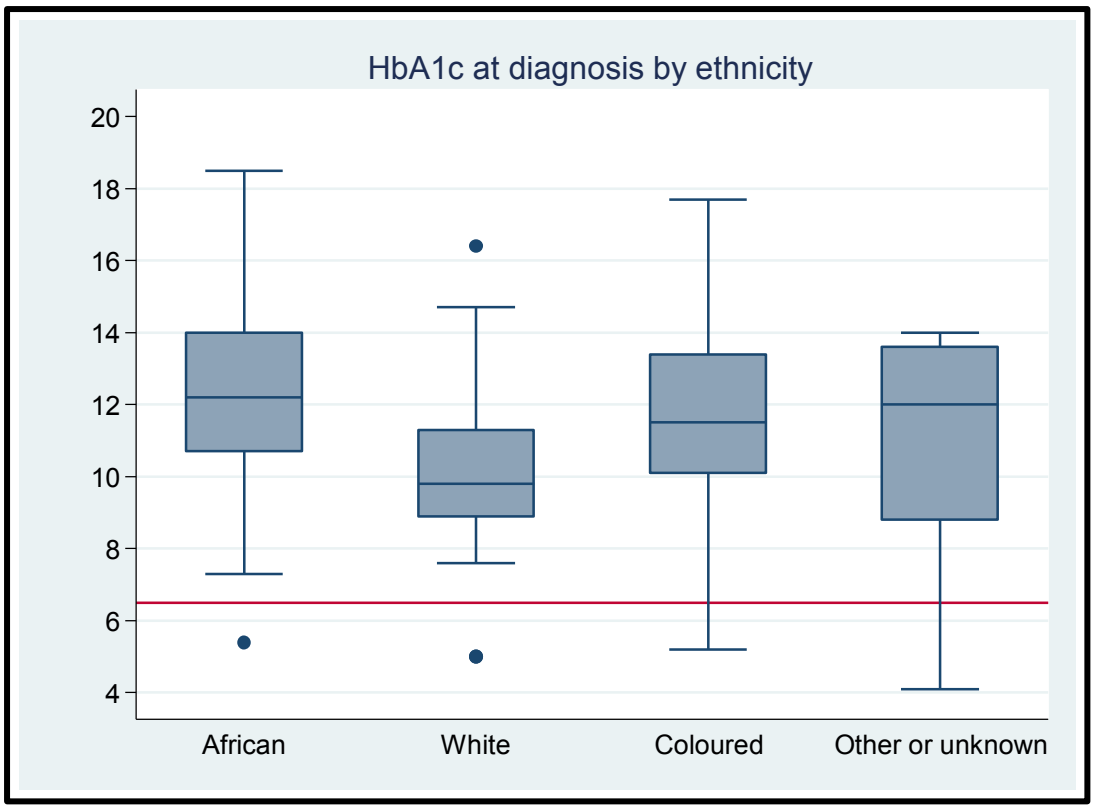

Figure 4: HbA1c according to ethnicity.

Hba1c values on y-axis expressed as %. The red line indicates the HbA1c value accepted as normal or non-diabetic.

CHAPTER 4

Contents:

1. Discussion

The aim of the study was to describe the characteristics of children presenting with DM from our referral centres and to compare them to the children in the rest of the world. Due to the lack of a diabetes registry in South Africa, the incidence and prevalence of DM in children from our area could not be calculated. It was anticipated that there would be an increase in the number of children diagnosed per year. This trend was not evident from the data. It is possible that the number of newly diagnosed patients is really around 40 per year in our region but the possibility is also that not all the newly diagnosed patients are referred to the diabetic centre at RCWMCH. The latter is probably more likely. Additionally, some children may be misdiagnosed and die before the diagnosis of DKA or DM could be made. A prospective study that includes data from all the referring facilities and private institutions will be of great value to ascertain the true number of newly diagnosed children as well as the incidence of DM.

Of the 225 patients included in the cohort over the 5-year period studied (2005-2009), almost half were from the lower income group. A third of the children were from the private sector or from higher income groups. Most (43%) of the children referred from the private sector were Caucasian and 35% Coloured. Even though most of the patients diagnosed in private are referred for diabetic education and review by a Paediatric Endocrinologist, it is possible that some of the patients diagnosed by General Paediatricians, might have not been included into the study. With that taken into account and the fact that RCWMH is a Public Sector facility, it explains the high number of children from lower income groups in the cohort. It would be useful to do a follow up prospective study to compare the quality of care the children in both sectors received and the number of visits to the facilities before the diagnosis was made.

A quarter of our patients were younger than 5 years old at the time of diagnosis. Half of the children in this group were patients form higher income families and 50% were Caucasian (Figure 2). The question remains whether the disease presents earlier in the Caucasian population or whether the patients of other ethnicity in this age group were misdiagnosed or never got referred. Further research will be required to ascertain whether this is in fact the case. 20% of the children less than 5 year of

age were already overweight or obese. An increase in BMI is directly linked to an increase in the incidence of diabetes (Waldhör, Schober, & Rami, 2003). The figures on obesity in children in South Africa are not known but from the data collected in this study 30% of the children in the older group were also obese or overweight.

A seasonal variation was observed at diagnosis similar to what is seen in the rest of the world. There were a higher number of newly diagnosed patients during autumn and winter (Elamin et al,1992; Habeb et al, 2011; Galler et al, 2010; Diamond group, 2006). This will fit with the hypothesis of viral infections acting as the 'tipping point' to start the cascade of events in individuals who already has auto-inflammation of the pancreas (Eurodiab,2000). Molchanova, Schreier, Lammi and Karvonen concluded that patients from centres further away from the equator were more likely to exhibit a seasonal pattern. Unfortunately, most of the information in their study was from the Northern hemisphere (Molchanova *et al*, 2009). They found a peak during winter months and through summer.

Antibody testing was only performed since 2008. From the results that were available, more children tested positive for anti-GAD than islet cell auto antibodies. 28 patients tested positive for both antibodies. Eight of the type 2 diabetes patients had antibody testing done. One tested positive for ICA antibodies and two tested positive for anti-GAD antibodies (Table 5). It is not known to the investigator whether these patients were later re-classified into the Type 1 rather than type 2 group. It might be useful to do antibody testing in order to make a diagnosis but it must be kept in mind that the phenotype might change at follow up (Unnikrishnan *et al*, 2008; Tfayli, Arslanian, 2009).

A concern that became evident from the study was that a large proportion (more than half) of patients presented in DKA that is a life threatening complication of Diabetes Mellitus (Table 3) (Wolfsdorf et al, 2014). The assumption can be made that there was a delay in making the diagnosis or delay in seeking medical assistance. The average HbA1c levels ranged from 9.5-12%. This is even more surprising if one takes into consideration that two thirds of the patients had a close relative living with DM. Two thirds of the children in the young group presented in DKA and had a mean HbA1c of 9.5%. These figures may even be higher as information at the time of presentation were lacking in quite a number of these patients.

The study had several shortcomings. Due to the retrospective nature of the study, vital information was not available in all instances. A prospective study will be more valuable to evaluate for instance the onset of symptoms and the duration of symptoms before presentation. Demographic information could also be verified when data is collected.

2. Conclusion

Diabetes Mellitus is not uncommon in South African children but a registry for diabetic children in South Africa is urgently needed in order to properly plan for their health care. Health Care workers need more education and awareness campaigns to consider a diagnosis of DM in children to avoid the complication of DKA at presentation. Public awareness is similarly required to ensure that symptoms of diabetes will be recognized timeously.

There was no conflict in interest in gathering the information for the study.

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APPENDICES

Appendix A

International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines 2009 Compendium

Paediatric Diabetes2009:10(Suppl. 12):3-12

Criteria for the diagnosis of diabetes mellitus:

1. Symptoms of diabetes plus casual plasma glucose concentration ≥11.1 mmol/L (200 mg/dl)∗.

Casual is defined as any time of day without regard to time since last meal.

or

2. Fasting plasma glucose ≥7.0 mmol/l (≥126 mg/dl).†

Fasting is defined as no caloric intake for at least 8 h.

or

3. 2-hour post load glucose ≥11.1 mmol/l (≥200 mg/dl) during an OGTT.

The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g.

∗Corresponding values (mmol/L) are ≥10.0 for venous whole blood and ≥11.1 for capillary whole blood and

†≥6.3 for both venous and capillary whole blood

Craig et al.

Clinical characteristics of type 1 diabetes, type 2 diabetes and monogenic diabetes in children and adolescents

Characteristic	**Type 1**	**Type 2**	**Monogenic**
Genetics:	Polygenic	Polygenic	Monogenic
Age at onset:	6 months to young adulthood	Usually pubertal	Often post pubertal except Glucokinase and neonatal diabetes
Clinical presentation:	Most often acute, rapid	Variable; from slow, mild (often insidious) to severe	Variable (may be incidental in glucokinase)
Associations: Autoimmunity Ketosis Obesity Acanthosis nigricans	 Yes Common Population frequency No	 No Uncommon Increased frequency Yes	 No Common in neonatal diabetes, rare in other forms Population frequency No
Frequency (% of all diabetes in young people)	Usually 90%+	Most countries <10% Japan 60-80%)	?1-3%
Parent with diabetes	2-4%	80%	90%

Definition of diabetic ketoacidosis (DKA):

The **biochemical criteria** for the diagnosis of DKA are:

• Hyperglycaemia (blood glucose >11 mmol/L [≈200 mg/dL])

• Venous pH <7.3 or bicarbonate <15 mmol/L

• Ketonaemia and ketonuria.

Pediatric Diabetes 2009: **10** (Suppl. 12): 118–133

Appendix B

HbA1c testing:

HbA1c tests were performed on capillary blood samples in a DCA analyser that is situated in the diabetes clinic at RCWMH.

Product information and certification is available at:

http://www.healthcare.siemens.com/point-of-care/diabetes/dca-vintage-analyzer.

The Analyser is calibrated weekly.

Appendix C

DATA CAPTURE SHEET:

DATE:_____(month/year)_____

Folder number					
DOB (yr-mo-d)					
Sex	M		F		
Address/ Area code					
Socio-economic status	H0	H1	H2	H3	
Date of Dx (yr-mo-d)					
Age at Dx (yr)					
HbA1c at Dx					
2nd HbA1c					
Date of 2nd HbA1c					
Antibodies	Pos	Neg	Unknown		
Weight (kg)					
2nd weight					
Height (cm)					
2nd height					
BMI					
2nd BMI					
Type of insulin (Regime)	1	2	3	4	5
Insulin/kg/d (IU/kg/d)					
Family history	Yes		No		

Insulin regimes:

1- Ultra-short acting
2- Short acting
3- Long acting
4- Biphasic
5- Basal bolus

Appendix D

Letter addressed to Groote Schuur Hospital

Dr AM Botes

Staines Road 8

Plumstead

7800

Tel: 0836319528

E-mail: mariebotes@hotmail.com

31 October 2011

Attention: Dr Kirsten

Re: MMED research

I hereby request permission to request the folders of all the newly diagnosed diabetics admitted to G25 at Groote Schuur Hospital from January 2005-December 2009. The data collected will be used anonymously and is for the purpose of an MMED project with the title: The incidence of newly diagnosed diabetes at RCWMCH from 2005-2009. Due to the fact that most diabetics are admitted to the diabetic service at GSH, the information at admission will also be needed.

Kind Regards

AM Botes

Student number: BTSALI001

Appendix E:

Letter addressed to RCWMCH

Dr AM Botes

Staines Road 8

Plumstead

7800

3 August 2011

Attention: Dr T Blake

Re: MMED research

I hereby request permission to review the folders of all the newly diagnosed diabetics seen at the diabetic clinic during the period 2005-2009. The data collected will be used anonymously and is for the purpose of a MMED project by the title: Demographic and laboratory characteristics of children, newly diagnosed with Diabetes from 2005-2009 at Red Cross War Memorial Children's Hospital.

Please see the attached letter of ethical approval from the UCT Human Research Ethics Committee.

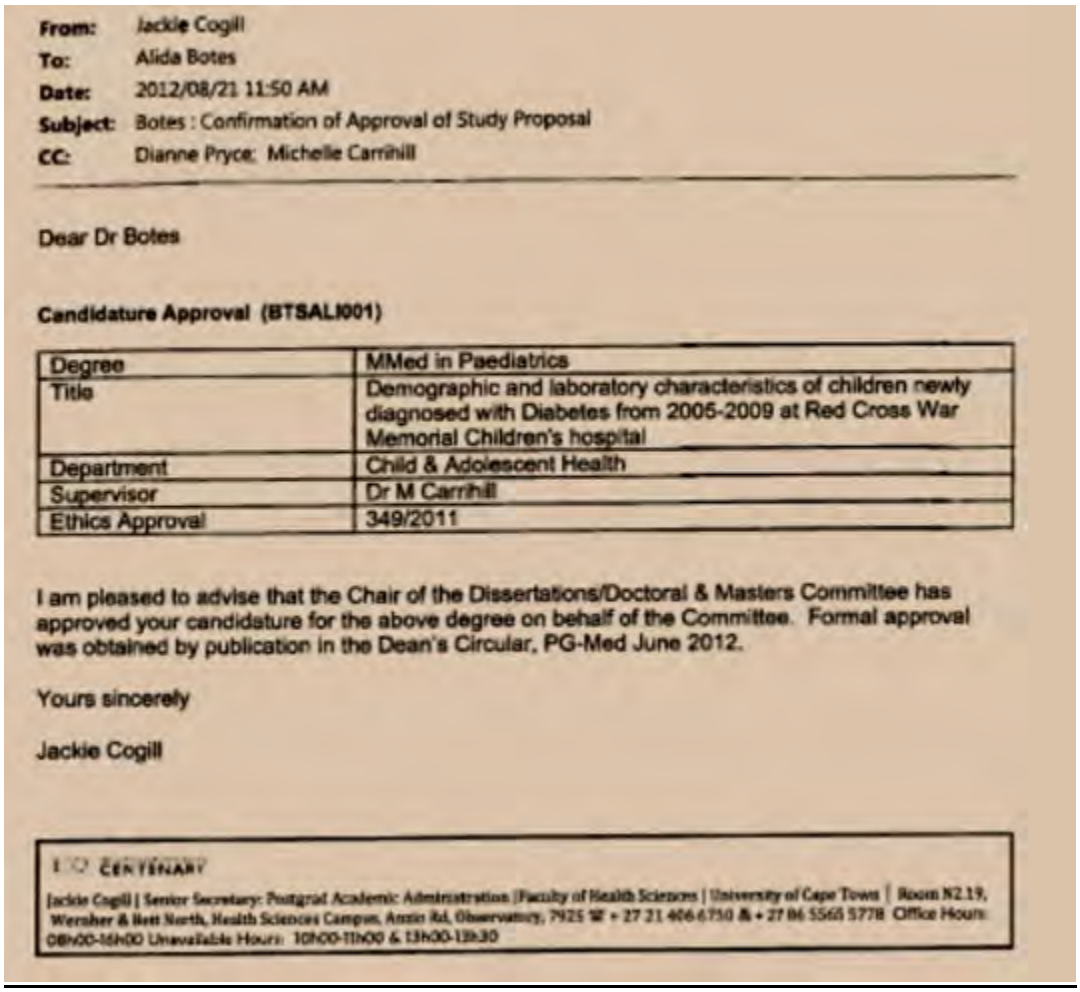
Kind Regards

AM Botes

Student number: BTSALI001

Appendix F

Ethics approval letter



From: Jackie Cogill
To: Alida Botes
Date: 2012/08/21 11:50 AM
Subject: Botes : Confirmation of Approval of Study Proposal
CC: Dianne Pryce; Michelle Carrihill

Dear Dr Botes

Candidature Approval (BTSALI001)

Degree	MMed in Paediatrics
Title	Demographic and laboratory characteristics of children newly diagnosed with Diabetes from 2005-2009 at Red Cross War Memorial Children's hospital
Department	Child & Adolescent Health
Supervisor	Dr M Carrihill
Ethics Approval	349/2011

I am pleased to advise that the Chair of the Dissertations/Doctoral & Masters Committee has approved your candidature for the above degree on behalf of the Committee. Formal approval was obtained by publication in the Dean's Circular, PG-Med June 2012.

Yours sincerely

Jackie Cogill

UCT CENTENARY
Jackie Cogill | Senior Secretary: Postgrad Academic Administration |Faculty of Health Sciences | University of Cape Town | Room N2.19, Wernher & Beit North, Health Sciences Campus, Anzio Rd, Observatory, 7925 W + 27 21 406 6750 & + 27 86 5565 5778 Office Hours: 08h00-16h00 Unavailable Hours: 10h00-11h00 & 13h00-13h30