DIABETIC MICROVASCULAR COMPLICATIONS IN TYPE 1 DIABETIC CHILDREN AND ADOLESCENTS ATTENDING THE CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL (CHBAH) PAEDIATRIC DIABETIC CLINIC

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Declaration

I, Sarah Berkenfeld, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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Sarah Berkenfeld

_____day of_____2016 in Johannesburg

Dedication

To the family, friends and patients who have encouraged me in my work.

Abstract

Background: Diabetic retinopathy and nephropathy are common complications in patients with insulin dependent diabetes mellitus (IDDM). This study describes the prevalence of these microvascular complications and their associated risk factors in children with IDDM, attending the Chris Hani Baragwanath Academic Hospital (CHBAH) between June 2015 and January 2016.

Methods: Participants between 9 and 19 years were screened for diabetic retinopathy and nephropathy using indirect ophthalmoscopy and random urine albumin to creatinine ratios respectively. Demographic, anthropometric, disease related and biochemical characteristics were described.

Results: The mean age of the participants was 11,96 years and the mean duration of diabetes was 1,88 years. The mean HbA1c was 12,4%, and 67,7% of admissions were due to DKA. Of the 34 children with IDDM, confirmed nephropathy was found in one participant. No new retinopathy was diagnosed and one participant was known to have cataracts. However, 26,5% of participants defaulted retinal screening.

Conclusions: Notwithstanding the finding that the patients in the cohort have poorly controlled diabetes (as ascertained by their HbA1c levels), a low prevalence of diabetic complications (ie. nephropathy and retinopathy) was found. This may be explained by the short disease duration in the study population. A young age at diagnosis and poor glycaemic control indicates a cohort at high risk, who will require continued screening.

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Table of Contents **Page**

List of abbreviations

AAO	American Academy of Ophthalmology
AAP	American Academy of Pediatricians
ACR	Albumin creatinine ratio
ADA	American Diabetes Association
AER	Albumin excretion rate
BMI	Body mass index
BP	Blood Pressure
CHBAH	Chris Hani Baragwanath Academic Hospital
DBP	Diastolic Blood Pressure
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
DRS	Diabetic Retinopathy Study
EDIC	Epidemiology of Diabetes Interventions and Complications Study
EDTA	Ethylenediaminetetraacetic acid
ESRD	End Stage Renal Disease
ETDRS	Early Treatment Diabetic Retinopathy Study
GFR	Glomerular filtration rate

GH	Growth Hormone
HbA1c	Glycosylated Haemoglobin
HGT	Haemo-glucose test
HLA	Histocompatibility Leukocyte Antigens
Ht/age	Height for age
IDDM	Insulin dependent diabetes mellitus
IDF	International Diabetes Federation
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IGF	Insulin-like growth factor
IGFBP	Insulin-like growth factor binding protein
IQR	Interquartile range
ISPAD	International Society for Paediatric and Adolescent Diabetes
mmol/l	Millimole per litre
NHBPEP	National High Blood Pressure Education Program
NHLS	National Health Laboratory Service
NKF	National Kidney Foundation

SBP	Systolic Blood Pressure
SD	Standard Deviation
Scr	Serum creatinine
SI	Standard International
UKPDS	U.K. Prospective Diabetes Study
umol/L	Micromoles per litre
WHO	World Health Organisation
Wt/age	Weight for age

List of Figures Page

List of Tables Page

1.0 Background and Literature review

1.1 Epidemiology of Diabetes Mellitus

Diabetes Mellitus involves a complex of metabolic abnormalities resulting from chronic hyperglycaemia. Long term progression of the disease poses the risk of developing both microvascular and macrovascular complications with resulting health burdens incurred by the individual and the health care system[1, 2]. Children and adolescents are more likely to be diagnosed with insulin dependent diabetes mellitus (IDDM) or type 1 diabetes mellitus[3]. Although retinopathy, nephropathy, neuropathy and macrovascular disease are responsible for significant diabetes related morbidity and mortality, nephropathy and retinopathy are the most common complications in children[1, 3]. This study aims to identify the prevalence of microangiopathic diabetic complications, namely nephropathy and retinopathy and the associated risk factors in children and adolescents attending the Chris Hani Baragwanath Academic Hospital.

The International Society for Pediatric and Adolescent Diabetes (ISPAD) defines diabetes mellitus as a "group of metabolic diseases characterised by chronic hyperglycaemia due to defects in insulin secretion, insulin action or both."[4] The diagnosis of diabetes is made based on blood glucose and clinical assessment. The criteria used for diagnosis below, are based on World Health Organisation (WHO) and ISPAD guidelines[4, 5]:

- Symptoms of diabetes and a casual plasma glucose concentration of ≥11,1 mmol/l (200 mg/dl). Casual is defined as any time of day, without regard to the time since the last meal. Corresponding values (mmol/l) are ≥10,0 mmol/l for venous whole blood and ≥11,0 mmol/l for capillary whole blood.

or

- Fasting plasma glucose ≥7,0 mmol/l (≥126 mg/dl). Fasting is defined as no caloric intake for at least 8 hours. Corresponding values are ≥ 6,3 mmol/l for both venous and capillary whole blood

or

- 2-hour post load glucose ≥11,1 mmol/l (≥200 mg/dl) during an oral glucose tolerance test (OGTT).The test should be performed, as described by WHO, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water or 1,75 g/kg of body weight to a maximum of 75g.

IDDM is characterised by an effective deficiency in insulin secretion due to pancreatic beta-cell damage[6, 7]. The causes of beta-cell destruction are multifactorial and involve autoimmunity, genetic susceptibility and environmental factors. The prevalence of auto-antibodies, anti-insulin, islet cell and glutamic acid decarboxylase enzyme antibodies in Western Caucasians has shown to be 60%, 70%, and 85% respectively[7]. Limited African and particularly South African data has suggested a slightly lower (44%) prevalence of auto antibody positivity[8, 9]. A variety of Histocompatibility Leukocyte Antigens (HLA) confers susceptibility to disease whilst the environmental triggers that are responsible for the disease process are unclear[6, 9, 10].

Western statistics report that 90% of childhood diabetes is insulin dependent and approximately 80 000 children worldwide, under 15 years of age, are predicated to develop IDDM annually[6]. The International Diabetes Federation Europe Region (EUR) reported in 2013, a prevalence of 129 350 cases of type 1 diabetes in children below the age of 14 years and an incidence of 20,4 per 100 000 per year[11]. South African data in 2013, according to the International Diabetes Federation (IDF) Diabetes Atlas (6th edition), reports the national diabetes prevalence at 8,4% and an incidence of type 1 diabetes of 0,8

per 100 000 in children aged 0-14 years. This is significantly lower than the statistics reported from Europe[12].

Even though clinically apparent disease occurs after 15-30 years of diabetes duration, structural and functional changes can be detected in early adolescence[1, 3]. It is thought that African populations are at greater risk of developing microvascular complications when compared to Caucasian populations[13-15]. Contributing reasons are poor glycaemic control, poor blood pressure control and genetic factors[13]. In a review of microvascular and macrovascular disease in Africa, Mbanya and colleague commented on the African diabetic population as a whole, including type 1 and type 2 diabetics. Studies from 15 countries were considered and variations in prevalence were influenced by clinical site, duration and diabetic control[2, 13]. This report draws attention to the high rate of complications that adds to the already overwhelming burden of communicable infectious diseases in the African region. The prevalence of diabetic retinopathy varied between 16% and 55%, diabetic nephropathy between 32% and 57% and the mean duration of diabetes was between 5 and 10 years[13]. Poor compliance and subsequent poor glycaemic control in this part of the world was significantly contributory. The difficulties in excluding the confounding factors of urinary tract infections and sickle cell anaemia were also acknowledged when analysing nephropathy.

Similarly, variations in the prevalence of complications between regions are described in table 1.1 below. Although the South African studies are adult based and look at mostly type 1 and type 2 diabetic patients, there is a high prevalence of diabetic nephropathy, retinopathy and poor glycaemic control. This translates into a considerable cost burden to the health care system since extensive management of these conditions is required. Detailed statistics on exclusively type 1 diabetic patients and childhood and adolescent diabetes from Africa, and particularly South Africa, are scarce. However, Tanzanian

children whose average HbA1c values are generally greater than 7,5% have a high prevalence of complications when compared to children in other regions, whose mean HbA1c values are between 8,3-8,8%. In the Tanzanian study only 1 child had an HbA1c value below 7,5% whilst 24,2% had values greater than 12,0%. This study suggests that in the African setting, the difficulties in achieving tight glycaemic control manifest as disease progression and mortality. International guidelines perhaps may not be applicable to the African setting as these patients are exposed to more significant hyperglycaemia. Well-timed screening for these complications is essential to identify pathology, implement early management and to prevent disease progression.

Table 1.1: Differences in diabetes complications, disease duration and glycaemic control between different regions

Author/ Reference Year	Type of Diabetes	n	Age group	Prevalence of microalbuminuria (%)	Prevalence of retinopathy (%)	Mean HbA1c[7] (SD[8])	Mean Duration Diabetes (SD)
Kalk, W.J. [15] 1994-2008 South Africa	Type 1	202	Adults	39,7 (African) 24,6 (Caucasian)	-	9,56 (2,57)	9,0 (5-15,3)[3]
Levitt, N.S.[16] 1992 South Africa	Mixed[1]	243	Adults	36,7 (29,0-44,7)[2]	55,4 (48-62,9)[2]	10,5 (2,9)	8 (8,1)
Rotchford, A.P.[17] 1999 South Africa	Mixed[1]	253	Adults	46,4 (40-53)[2]	40,3 (34,2-46,6)[2]	11,3 (3)	4,2 (6weeks-60years)[4]
Majaliwa, E.D.[18] 2005-2006 Tanzania	Type 1	99	Children (5-18 years)	29 (29,3)	22	-[5]	-[6]
Craig, M.E.[19] 2001-2002 Asia and Western Pacific	Mixed[1]	2312	Children	0,7	2,6	8,3 (7,4-9,7)[3]	4,4 (2,5-7,2)[3]
National Paediatric Diabetes Audit Report[20] 2013-2014	Mixed[1]	24 665	Children	7,1	14,1	8,7 (3,7)	-
El Samahy, M.H.[21] 2010 Egypt	Mixed[1]	936	Children	6,8	1,8	8,8 (4,6)	6,37 (3,6)
Donaghue, K.C.[22] 1997 Australia	Type 1	68	Children	8	9	8,4 (1,22)	3,6 (1,5-5,8)[3]

[1] Mixed-Patients with type1diabetes mellitus and patients with type 2 diabetes mellitus; [2]95% Confidence interval; [3]Median (Interquartile range); [4] Range;
[5] 60% of participants had an HbA1c between 7,5-10%, 38,3% had an HbA1c >10%; [6] 51,1% had a duration of diabetes of 1-5 years and 38,4% had a duration of > 5 years; [7]HbA1c-Glycosylated Haemoglobin, [8]SD- standard deviation

1.2 Risk factors for Microvascular Complications

Microvascular complications, nephropathy and retinopathy, have been associated with identifiable predisposing factors. It has been observed that despite sustained poor glycaemic control, at most only 40% of diabetic patients will develop diabetic nephropathy. This suggests that although not modifiable, genetic susceptibility is significant[14, 23]. Independent modifiable risk factors for the development of diabetic nephropathy are sustained hyperglycaemia and hypertension[14, 15, 24]. When considering nephropathy on its own, dyslipidemia, gender and BMI are also relevant risk factors, although gender and BMI are inconsistent in their relationship to nephropathy and retinopathy across studies[14, 15, 25-27]. The land mark Diabetes Control and Complications Trial (DCCT) and the follow up Epidemiology of Diabetes Interventions and Complications Study (EDIC) provided undisputed evidence that intensive insulin therapy with good glycaemic control (HbA1c median 7%) reduced the risk of diabetic nephropathy and retinopathy when compared to conventional therapy and higher HbA1c values (median 9%)[28, 29].

Studies investigating diabetic retinopathy have identified glycaemic control (HbA1c), duration of disease, puberty, blood pressure control and increased body mass index (BMI) as risk factors for the development of diabetic retinopathy in patients with type 1 and type 2 diabetes mellitus[27, 29-33]. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) looked at 955 patients with IDDM and found that increased risk of proliferative diabetic retinopathy was associated with more severe retinopathy at baseline, higher HbA1c, greater BMI and a rising HbA1c value in the defined period of study[34].

Age of diabetes onset and longer diabetes duration are well described risk factors for the development of microvascular complications[35, 36]. The pre-pubertal duration of

hyperglycaemia has been shown to have a lesser effect than post pubertal duration on the time to development of microangiopathic complications[1, 23, 27, 35, 37, 38]. The pubertal period in itself has been described as a period of increased risk for diabetic microangiopathy[3, 23, 27, 36]. The poor glycaemic control that occurs during the pubertal years of diabetes contributes to the development of microvascular diabetes complications. Psychosocial issues that occur in the pubertal years and subsequent poor compliance are not the only factors implicated[39]. The complex hormonal and physiological processes that tend to occur during puberty cause insulin resistance and hyperglycemia[27]. Specifically, changes in the growth hormone/insulin like growth factor 1 (GH/IGF-1) axis, adiposity and sex hormones are responsible for the effective decrease in insulin sensitivity during this time[3, 27, 40].

1.3 Diabetic Nephropathy

Diabetic nephropathy is defined as persistent proteinuria > 500mg/24 hours or albuminuria > 300mg/24 hours, associated with hypertension and a diminishing glomerular filtration rate (GFR) [1, 14, 41]. "Incipient nephropathy", as evident by persistent microalbuminuria is defined, in timed urine collections, by an albumin excretion rate (AER) between 20 and 200ug/min or AER between 30 and 300 mg/24 hours. In early morning and random spot specimens, albuminuria is defined by an albumin concentration of 30-300mg/L or an albumin creatinine ratio (ACR) of 2,5-25mg/mmol in males and 3,5-25 mg/mmol in females[1, 41, 42]. Persistence is demonstrated by at least two out of three specimens showing abnormal values over a 3 to 6 month period.

Clinically apparent renal disease is preceded by a period of early nephropathy marked by microalbuminuria, initially supernormal glomerular filtration rate (GFR) and rising blood pressure (BP)[42]. Microalbuminuria predicts diabetic nephropathy and in itself correlates with retinopathy and mortality[42-44]. As such it presents an intermediary point at which

effective intervention can slow the course of disease and prolong the time to developing end stage renal disease[45, 46].

Pathological changes that occur in the kidney, progress slowly over a long period of time during which proteinuria is undetectable. A significant portion of patients demonstrate initial glomerular hyperfiltration which is thought to be due to an increased glomerular filtration pressure[43]. This increased filtration pressure causes glomerular damage, a declining GFR, albuminuria and ultimately end stage renal disease (ESRD) [42, 46]. Although the earliest sign of developing nephropathy is microalbuminuria, it is thought that a progressive decline in GFR occurs prior to the development of microalbuminuria. Research in this area is limited [42-44, 46]. It is important to note that not all patients with microalbuminuria will progress to overt nephropathy and ESRD, rather some may revert to normoalbuminuria[44, 46].

Diabetic renal disease remains a significant cause of morbidity and mortality not only in South Africa but internationally too, with nephropathy and subsequent renal failure being a major cause of death in adult patients with type 1 diabetes[1, 15, 41, 46, 47]. The U.K. Prospective Diabetes Study (UKPDS) reported in 2005, a prevalence of proteinuria in 15-40% of type 1 diabetic adults with a peak incidence after 15-20 years of diabetic duration[14]. A South African based study of urban African adults with type 1 diabetes reports a prevalence of microalbuminuria of 39,7% in African patients and 24,6% in Caucasian patients with a mean duration of 8 and 10 years respectively[15]. This suggests that African patients are at higher risk of developing microalbuminuria after shorter disease duration when compared to European patients. Microalbuminuria, which predicts diabetic nephropathy, correlates with retinopathy and mortality[42-44].

Screening guidelines for microvascular complications recommend urine screening after 3 to 5 years of diabetes duration[1, 14, 48]. However in the presence of poor glycaemic, lipid and blood pressure control, the prevalence of microalbuminuria before 5 years of duration has been shown to reach up to 18%[14].

The reference ranges used for detecting microalbuminuria have been described above and whilst 24 hour urine albumin excretion measurements have previously been regarded as the gold standard, they are generally cumbersome and inconvenient to the patient[49, 50]. First early morning urine specimens have shown a good correlation with 24 hour urine albumin excretion and have been recommended for children, to prevent results being influenced by the effects of orthostatic hypotension[50, 51]. Although early morning specimens are preferable, the American Diabetes Association (ADA) guided by the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) accepts the use of an untimed spot urine collection for measurement of albumin creatinine ratio as a replacement for 24 hour urine albumin excretion[50, 52].

The K/DOQI also advises that patients at high risk for albuminuria, especially diabetic patients, should be screened with a random urine albumin creatinine ratio (UACR) despite testing negative for protein on a standard urine dipstick test[52].

It is important to note that a raised ACR may be confounded by other causes of raised albumin excretion such as the effects of exercise within 24 hours, infection, fever, congestive cardiac failure, marked hyperglycaemia (ketotic states) and marked hypertension[49, 50]. In children with a short duration of diabetes and microalbuminuria, one should exclude other causes of nephritis which are common in children[1]. A reliable diagnosis of persistent microalbuminuria requires two out of three specimens, over a three to six month period to be abnormal[49, 50, 52].

1.4 Diabetic Retinopathy

Diabetic retinopathy is a major cause of morbidity in diabetic patients, and is the leading cause of blindness in most Western populations, particularly in young adults[53]. The pathophysiology behind retinopathy involves polyol accumulation, advanced glycosylation end products, oxidative stress and activation of protein kinase C[54]. Retinal changes progresses from mild, moderate and severe non-proliferative abnormalities to proliferative retinal disease[55].

Diabetic retinopathy is uncommon within the first three to five years of diabetes duration and very few cases have been reported in children less than 10 years of age. However, after 20 years of disease duration nearly all patients develop retinopathy[56].

The screening guidelines proposed by different associations namely the American Academy of Ophthalmology (AAO), The American Diabetes Association (ADA), The American Academy of Pediatricians (AAP) and ISPAD, attempt to implement a program which allows for the detection of sight threatening retinopathy as early as possible in order to promptly provide the appropriate management strategy. In earlier guidelines the optimal time for the first screening varied from 9-10 years of age and 3-5 years of diabetes duration[53]. More recent studies advocate screening from a later age with longer diabetes duration[1, 57-59].

ISPAD guidelines advise the diagnosis and screening for diabetic retinopathy using bimicroscopic fundus slit lamp examination through dilated pupils, by an ophthalmologist or optometrist and mydriatic seven field stereoscopic retinal photography[1]. Digital retinal photography, dilated direct and indirect ophthalmoscopy are also acceptable methods of screening[1, 57, 58]. The grading of seven field stereoscopic colour photographs according to the Early Treatment Diabetic Retinopathy Group (ETDR) is considered the gold standard.

However, it requires a trained photographer, a trained reader, is technical and laborious to use and is more practical in a research rather than a clinical setting[1, 31, 54]. In order to simplify this process and develop a clear consensus between clinicians worldwide, the International Clinical Disease Severity Scale for Diabetic retinopathy was created and is based on the findings of Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) and ETDRS[60]. See table 1.2.

Table 1.2: International Clinical Diabetic Retinopathy Disease Severity Scale (American Academy of Ophthalmology 2002)

Proposed Disease Severity Level	**Findings observed upon dilated ophthalmoscopy**
No Apparent Retinopathy	No abnormalities
Mild Non-proliferative Diabetic Retinopathy	Micro-aneurysms only
Moderate Non-proliferative Diabetic Retinopathy (NPDR)	More than just aneurysms but less than severe NPDR
Severe Non-proliferative Diabetic Retinopathy (NPDR)	Any of the following: • More than 20 intraretinal haemorrhages in each of the four quadrants • Definite venous beading in two or more quadrants • Prominent IRMA (intraretinal microvascular abnormalities) in one or more quadrants **And** no signs of proliferative retinopathy
Proliferative Diabetic Retinopathy	One or both of the following: • Neovascularization • Vitreous/pre-retinal haemorrhage

The prevalence and incidence of diabetic retinopathy has been described in several studies with an emphasis on duration of diabetes at the time of diagnosis[61]. A study of 557 Asian Indian patients with a median age of 14,6 years (IQR: 12,4-17,0) and median diabetes duration of 8 years (IQR: 5,5-9,9) found a prevalence of retinopathy of 14,5%[62]. A similar

prevalence of 14,5%, was shown in Sweden in patients with a median age of 16,8 years (IQR: 13,6-20,3) and a median diabetes duration of 8 years (IQR: 6,0-9,4)[62]. The SEARCH study evaluated patients diagnosed less than 20 years of age and reported a prevalence of 17% when controlled for age, duration and HbA1c level[32].

It is generally accepted that retinopathy is rare in children less than 9 years, before puberty and in the first 3-5 years of disease duration[31, 53]. A recent study in Philadelphia reviewed 370 type 1 and type 2 diabetic children with a mean age of 11,2 years (1,0-17,5) and diabetes duration 5,2 years (0,1-16,2). The authors reported that no children had diabetic retinopathy and 12 children had cataracts. Those with cataracts were diagnosed based on symptoms rather than screening methods[63]. Nevertheless there are reports of younger prepubertal children developing retinal changes as early as 5,5-9,5 years with disease duration less than 1,5-2,2 years[22, 62, 64]. In view of these studies and of the poor glycaemic control noted in African populations, our study considered the lowest end of the age spectrum when screening for retinal and renal changes.

With the knowledge that improved glycaemic control and retinal photocoagulation slows the progression to visual loss, the early detection of retinal changes is an important part of holistic diabetes care. The DCCT showed that tight glycaemic control reduced or prevented the development of retinopathy by 27% and reduced the progression of existing retinopathy by 34-76%[28].

The Diabetic Retinopathy Study and the Early Treatment Diabetic Retinopathy Study (ETDRS) have shown that panretinal photocoagulation reduces severe visual loss when performed at the appropriate stage of proliferative retinopathy and maculopathy[65, 66]. Although it does not return vision to normal, laser photocoagulation slows the progression of retinal disease and reduces visual loss[31].

The guidelines for screening and managing childhood and adolescent diabetes have been developed using predominantly Western Caucasian-based population data. Limited data exists on the prevalence and incidence of microvascular complications in African children and as such current management is guided by the literature and recommendations adopted from ISPAD and ADA guidelines[1, 39, 49, 57-59, 67-69]. This study aims to evaluate the prevalence of nephropathy and retinopathy and the presence of known risk factors in children and adolescents (9-19 years) with type 1 diabetes, attending the Chris Hani Baragwanath Academic Hospital, Paediatric Endocrine clinic.

1.5 Objectives

The primary objectives of this study are:

1. To evaluate the prevalence of complications related to retinopathy and nephropathy in a cohort of type 1 diabetic patients attending the Chris Hani Baragwanath Academic Hospital, Paediatric Diabetic clinic from 9 to 19 years of age (with unspecified duration of diabetes).

The secondary outcomes of this study are:

1. To evaluate the known factors associated with these complications:
    - Age of onset
    - Duration of diabetes
    - Glycaemic control
    - Pubertal status
    - BMI
2. To determine factors associated with glycaemic control:
    - Insulin regimen

- Compliance - based on HbA1c

3. To evaluate epidemiological data relating to the presence of diabetic disease and its complications:
    - Gender
    - Race

2.0 Research Design and Methods

2.1 Study Design

This prospective descriptive study took place at the Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto, South Africa between May 2015 and January 2016. During this time children and adolescents between 9 and 19 years, attending the paediatric endocrine clinic and some patients admitted to the paediatric wards were included. All participants had been previously diagnosed as having IDDM by their treating paediatrician and/or endocrinologist.

2.2 Inclusion and exclusion criteria

All patients meeting the age criteria of 9 to 19 years and who agreed to participate were included in the study. Patients who had features suggestive of metabolic syndrome were also included as they were insulin dependent and had a young age of disease onset in keeping with type 1 diabetes. Critically ill patients admitted in the paediatric wards were excluded unless they had recovered from the current acute illness.

2.3 Study Setting

Chris Hani Baragwanath Academic Hospital (CHBAH) is situated in Southern Gauteng, South Africa. It is a tertiary level academic hospital affiliated with the University of the Witwatersrand and mainly serves the peri-urban area of Soweto which has a population of about one million people. It is the third largest hospital in the world, with approximately 3200 beds. Every year, about 150 000 inpatient and 500 000 outpatients are seen[70]. St John Eye Hospital, where retinal screening is performed, is where the Department of Ophthalmology provides 111 beds and counts about 50 000 patients per year.

Soweto, which stands for South Western Township, is an area rich in history and cultural diversity. The people who live there are mainly Black Africans and although during Apartheid there was limited planning for infrastructure, this is rapidly changing. People live in classically government built "match box" four bedroom houses, tin shanties and more affluent modern homes, indicating an ever increasing range of socioeconomic conditions.

The patients attending this hospital and particularly this clinic are representative of the South African population as a whole. Mayosi and colleague described the South African people "20 years after Mandela" to be living in poverty, with 23% below the food poverty line and 54% lacking food security. Health care resources are also severely constrained with 84% of the population being uninsured and receiving care from only 30% of the country's doctors. This is occurring in the face of an increasing prevalence of non-communicable diseases, which together with the already existing infectious diseases and violent injuries, places a major burden on the health care system[71].

The participants in this study are children with already diagnosed IDDM and who are referred from the general paediatric admission wards and outpatient clinics at CHBAH. They are also patients referred from private general practitioners, specialist practices and lower level health care facilities from areas as far as Klerksdorp. Those seen at our institution, all have access to home glucose monitoring. They are children of school going age who are subject to the above described financial difficulties. Their access to health care and healthy living is dictated by distances between their homes and the hospital and the financial cost of this. They are subject to the inconsistent availability of healthy food, and a lack of support by family members who have a limited understanding of their disease. Although these children may not be living classically third world lifestyles, the described

socioeconomic difficulties they face, place them at the mercy of the health care burden of the third world.

The paediatric endocrine clinic at CHBAH strives to achieve international standards of care within a resource limited setting. The clinic is run by paediatric endocrinologists and is staffed by dieticians and nursing staff experienced in the field of diabetes and who assist in counselling patients and their families. The clinic is inconsistently provided with an HbA1c point of care system from the hospital's laboratory and is stocked with glucometers, urine dipsticks, a stature meter, weight scale and a fully equipped resuscitation trolley. Blood and urine specimens, are sent to the National Health Sciences Laboratory (NHLS) which is on site. Patients requiring admission are directly transferred to the paediatric admission ward, staffed by qualified paediatricians, registrars, medical officers and interns in training. Although severely limited by bed numbers, if required, there is a specialised paediatric intensive care unit at CHBAH.

Patients are seen at the clinic every 3 to 6 months by specialist paediatric endocrinologists. They do, however, default their appointments from time to time citing reasons ranging from lack of transport, funds, school commitments and work commitments of the accompanying caregiver.

2.4 Study Methods

Participants were enrolled for the most part during their routine appointments at the diabetic clinic. Two participants were enrolled from the paediatric ward after their acute conditions had resolved. The participants and their parents were interviewed and examined by the investigator in addition to the routine examination by the specialist. Prior to any investigation, consent was obtained from parents, assent was obtained from participants and ethical approval was granted by the University of the Witwatersrand Ethics

Committee. Both parents and participants were given age appropriate information sheets which explained the reasons for the study, the details of the procedures and their rights as participants.

The routine measurements taken by the diabetic clinic nursing staff were recorded in data collection sheets. These included spot finger prick haemoglucose tests, urine dipsticks and weight in kilograms (kg). Urine was tested using Makromed urine test strips and spot capillary blood for glucose was tested using an Accu-Check Active glucometer.

In addition to these measurements the investigator measured each participant's height and blood pressure and assessed pubertal status, according to the Tanner classification. Blood was taken for HbA1c, urea and creatinine and urine was sent for albumin creatinine ratio. The participant and his/her parent were interviewed in order to assess the number of times the participant had been admitted and the reasons for admission. If this was unclear, further information was found in the participant's outpatient and diabetic files.

The participant's current age, gender, race, age of onset and duration of diabetes were collected from the patient file or on questioning. Age at diagnosis was recorded as the day of initial presentation to a hospital (if requiring admission) or the first contact with a health care provider. This was either at CHBAH or at other referring facilities in the government or private sector. If the exact date was not available or known, the first day of the known month was used as a marker. The duration of diabetes was calculated as the difference between the date of interview and the date of diagnosis.

Other disease related variables were recorded as co-morbid diagnoses, insulin regimen and previous glycosylated haemoglobin (HbA1c) levels reported as a percentage (%).

The insulin regimen used was that which the attending endocrinologist prescribed at that particular visit. In accordance with the DCCT, an intensive regimen consisted of three or

more injections per day in conjunction with home glucose monitoring, whilst a conventional regimen consisted of two or less injections per day[28, 29].

The first HbA1c referred to the very first documented HbA1c available for each participant, found either by reviewing the diabetic files or by searching against the participant's patient file number on TrakCare Lab Webviewer, the results management system used by the National Health Laboratory Service (NHLS).

2.4.1 Study Procedures

2.4.1.1 Anthropometry

Weight was obtained using the same digital scale for every participant and measured in kilograms (kg). Height measured in centimetres (cm), was measured using a Panamedic Stature Meter. Body mass index (BMI) was calculated using the formula weight (kg) ÷ (height (m)) ^{2}. The z scores for height for age and BMI were obtained using the StatCoder Clinical Application for iPhone. This uses age and measured anthropometry to calculate exact z scores based on the WHO Child Growth Standards. Weight for age was calculated using the Centre for Disease Control and Prevention (CDC) growth charts according to the online "Children Growth Chart Calculator-weight for age percentile, 2-20 years."[72] The WHO classifies growth parameters according to z scores (see table 2.1-2.30)[73].

Table 2.1: WHO weight for age Z Scores for boys and girls

Growth Status	Weight for age (Z score)
Normal weight	-2 to +2
Underweight	-2 to -3
Severely underweight	<-3
Overweight	+2 to +3
Obese	>+3

Table 2.2: WHO Height for age Z Scores for boys and girls

Growth Status	Height for age (Z score)
Normal height	-2 to +2
Stunted	-2 to -3
Severely Stunted	<-3

Table 2.3: WHO BMI for age Z Scores for boys and girls

Growth Status	BMI for age (Z score)
Normal	-2 to +2
Wasted	-2 to -3
Severely Wasted	<-3
Overweight	+2 to +3
Obese	>+3

2.4.1.2 Pubertal staging

Pubertal staging was based on a physical examination by the primary investigator and correlated with the assessment performed by the attending paediatric endocrinologist in the clinic. The Tanner stages of puberty were used to assess stages of development[74]. The details of this staging system are specified in appendix 1. Puberty was considered as Tanner stage two and above. Tanner stage one was considered pre-puberty.

2.4.1.3 Blood Pressure

Blood Pressure was measured in a seated position, using a DuraShock Handheld Aneroid Sphygmomanometer. Although a "resting time" was not measured, the participants had been sitting in the waiting area of the clinic for at least 30 minutes and had been seated whilst the study procedures were explained and consent obtained. It was therefore assumed that the participant had rested for at least 5 minutes prior to measurements being taken. Cuffs ranging from infant to adult sizes were available and the correct cuff was used based on the National High Blood Pressure Education Program (NHBPEP) Working Group on

Children and Adolescents guidelines[75]. The auscultation technique was used and systolic blood pressure (SBP) was recorded at Korotkoff 1. Diastolic blood pressure (DBP) was recorded at Korotkoff 5. According to the NHBPEP guidelines the following definitions were used to classify blood pressure values as "normal", "pre-hypertension" or "hypertension".

- Hypertension: average SBP and/ or DBP greater or equal to the 95th percentile for sex, age, and height on three or more occasions
- Pre-hypertension : average SBP or DBP between the 90th and 95th percentile
- Normotension: SBP and DBP less than the 90th percentile for sex age and height

Abnormal values were flagged for the treating physician to follow up and investigate further.

2.4.1.4 Blood specimens

Two to five millilitres of venous blood were taken from each participant. The site of venipuncture was cleaned using 70% alcohol swabs (Webcol Alcohol Prep Pad or a generic brand depending on availability). A sterile disposable syringe and needle (22 or 23 gauge) was used for each patient. The blood was sent to the laboratory as EDTA (ethylenediaminetetraacetic acid) blood for HbA1c and clotted blood for urea, creatinine and electrolytes. The HbA1c result was reported as a percentage (%), urea was reported as millimoles per litre (mmol/l) and creatinine was reported as micromoles per litre (umol/l).

Serum and urine creatinine was analysed by the NHLS using a kinetic colorimetric assay based on the Jaffe method on Roche/Hitachi Cobas C systems. The laboratory reference ranges for creatinine are as follows:

Table 2.4: Reference ranges for serum creatinine by age

Age (years)	Creatinine (umol/l)	Creatinine (mg/dl)
7-9	35-53	0,40-0,60
9-11	34-65	0,39-0,73
11-13	46-70	0,53-0,79
13-15	50-77	0,57-0,87
>15	62-106	0,70-1,20

NICE guidelines recommend the use of HbA1c measurements that have been calibrated according to International Federation of Clinical Chemistry (IFCC) standardisation[59]. These values are reported as mmol/mol however the CHBAH paediatric department historically uses HbA1c values as a percentage, in accordance with National Glycohemoglobin Standardization Program (NGSP/DCCT) values[76]. In the 2011 ISPAD guidelines, HbA1c targets were grouped according to table 2.5 and when statistically analysed, HbA1c values in our study were grouped in the same way[69].

Table 2.5: Target indicators of glycaemic control according to the Global IDF/ISPAD Guidelines for Diabetes in Childhood and Adolescence

	Ideal HbA1c[1] (non diabetic)	Optimal HbA1c	Suboptimal HbA1c (action suggested)	High Risk HbA1c (action required)
DCCT[2] standardised (%)	<6,05	<7,5	7,5-9,0	>9,0
IFCC[3] (mmol/mol)	<43	<58	58-75	>75

[1]HbA1c-Glycosylated Haemoglobin; [2]-DCCT- Diabetes Control and Complications Trial; [3]IFCC- International Federation of Clinical Chemistry and Laboratory Medicine

2.4.1.5 Estimated glomerular filtration rate

Estimated glomerular filtration rate (eGFR) was calculated based on the bedside Schwartz equation (eGFR mL/min/1,73m^2= 0,41× height (cm)/Serum creatinine (mg/dl)) [77, 78]. Since the NHLS reports serum creatinine (Scr) as micromoles per litre (umol/l), the formula was modified to correct to standard international (SI) units using the conversion factor umol/l×0,0113=mg/dl. Reference ranges for GFR, according to the Schwartz formula, vary between studies and depending on what methods of creatinine measurements are used[79, 80]. The NKF guideline divides chronic kidney disease into five stages, with an additional category of "increased risk." "Increased risk" refers to patients with a GFR ≥ 60 ml/min/1,73m^2 and chronic kidney disease risk factors (older age, family history of chronic kidney disease, reduction in kidney mass, low birth weight, U.S. racial or ethnic minority status, low income or education) or initiation factors (diabetes, high blood pressure, autoimmune diseases, systemic infections, urinary tract infections, urinary stones, lower urinary tract obstruction, drug toxicity) [81]. Stage 1 kidney disease is classified by kidney damage, indicated by microalbuminuria, and a normal or increased GFR ≥90ml/min/1,73m^2. Stage 5 kidney disease is defined by a GFR≤ 15ml/min/1,73m^2 (or requiring renal replacement therapy). Normal values for GFR are given by the NKF/KDOQI guidelines (see table 2.6).

Table 2.6: Normal GFR in children and young adults according to KDOQI clinical practice guidelines for chronic kidney disease[81].

Age (years)	Mean GFR[1] ± SD[2] (ml/min/1,73m^2)
2-12	133,0 ± 14,8
13-21 (males)	140 ± 30,0
13-21 (females)	126 ± 22,0

[1]GFR-Glomerular filtration rate; [2]SD-Standard deviation

2.4.1.6 Urine Specimens

Random spot urine specimens were collected from every participant. The urine specimen used for the urine dipstick was used for the formal urine ACR unless the participant had accidentally discarded it. In this case the participant provided a new urine specimen with minimal time lapse between the two specimens. Urine albumin and creatinine were tested by the NHLS and reported as a urine albumin/creatinine ratio (UACR) in milligrams of albumin per millimole of creatinine (mg/mmol). Two samples were not correctly processed by the laboratory and only 32 urine samples were available for statistical analysis. UACR was reported as 0 mg/mmol if the urine albumin concentration was less than 3 mg. If the urine albumin was less than 3mg and the urine creatinine was less than the laboratory reference range for creatinine (375umol/l), the value was reported as "unable to calculate". In the statistical analysis, the values that were "unable to be calculated" were recorded as 0 mg/mmol as they effectively indicated no evidence of microalbuminuria. Microalbuminuria was defined as UACR 2,5-25 mg/mmol in males and 3,5-25 mg/mmol in females, in keeping with ISPAD guidelines[1]. The attending endocrinologists were notified of any abnormal UACR results, in order to facilitate appropriate further investigation.

2.4.1.7 Retinal Screening

An appointment at St John Eye Hospital was made for every participant. This was prearranged with Dr. H. Kana, an ophthalmologist at the centre. Retinal screening was performed by Dr. Kana or by one of the ophthalmology consultants or registrars working in the paediatric ophthalmology clinic, held every Friday. Indirect ophthalmoscopy was performed on each participant after both eyes had been dilated. Findings were recorded according to the International Clinical Diabetic Retinopathy Disease Severity Scale (table1.2). The ophthalmologists were provided with an instruction sheet and a

standardised check box findings sheet for recording their examination. Copies of the retinal examination were made using carbon paper at the time of the examination and the copied sheet was collected by the primary investigator.

2.5 Statistical Analysis

Descriptive statistics were used to analyse the baseline data characteristics. Distribution was normal if the Kolmogorov-Smirnov (KS) p>0,2 or Shapiro Wilk (SW) p>0,05. Parametric data was reported using the mean and standard deviation (SD) and comparisons were made using the Student's t test. Non parametric data was defined by a KS<0,2 or SW< 0,05 and was reported using the median and inter-quartile range (IQR). Comparisons were made using the Mann Whitney-U test. Categorical variables were described using frequencies and percentages and Fischer's exact test was used for comparisons. Two-tailed p values ≤ 0,05 were considered significant. Comparisons were made between participants grouped by duration of diabetes greater or less than 5 years, intensive or conventional insulin regimen and pubertal status respectively. All calculations were performed using the computer software Statistica, version 12, Copyright© Statsoft, 2014.

3.0 Results

3.1 Demographic characteristics

Thirty four children and adolescents between the ages of 9 and 19 years were studied from 1 May 2015 to 31 January 2016. The mean age at interview was 11,96 years (SD: 1,54) and the mean age at diagnosis was 9,9 years (SD: 3,19; see table 3.1). The median duration of diabetes was 1,88 years (IQR: 0,59-4,45). When assessing duration of diabetes, 23,5% (8) of the cohort had been diabetic for more than 5 years whilst 76,5% (26) had been diabetic for less than 5 years. There were no Caucasian patients however, 85,3% (29) of the participants were African and 14,7% (5) were of mixed ancestry. Gender analysis revealed that 35,3% (12) were males and 64,7% (22) were females.

The mean height of the cohort was 146,51cm (SD: 9,81) with a height for age (Ht/age) z score of -0,50 (SD: 1,24). The median weight was 38,25kg (IQR: 33,90-43,60) with a median BMI of 17,70kg/m^2 (IQR: 16,58-20,05) and a mean BMI z score of 0,17 (SD: 1.29). Puberty was diagnosed in 73,5% (25) of the cohort whilst 26,5% (9) were pre-pubertal (see table 3.1).

Table 3.1: Demographic characteristics of type 1 diabetic children and adolescents attending the CHBAH paediatric diabetic clinic

	n=34 (%)
Race	
African	29 (85,3)
Coloured	5 (14,7)
Caucasian	0
Gender	
Male	12 (35,3)
Female	22 (64,7)
Duration of Diabetes	
> 5 years	8 (23,5)
< 5 years	26 (76,5)
Age	
Mean (SD[1]) Age at Interview (years)	11,96 (1,54)
Mean (SD) Age at Diagnosis (years)	9,90 (3,19)
Median (IQR[2]) Duration of Diabetes (years)	1,88 (0,59-4,45)
Anthropometry	
Median (IQR) BMI[3] (kg/m2)	17,70 (16,58-20,05)
Mean (SD) BMI Z Score	0,17 (1,29)
Mean (SD) Height/Age Z Score	-0,50 (1,24)

[1]SD –standard deviation; [2]IQR-inter-quartile range; [3]BMI-body mass index

Glycaemic control

The point of care haemoglucose test at the time of enrolment was a mean of 13,27 mmol/l (SD: 6,37; see table 3.2). Two patients did not have a traceable baseline (first) HbA1c measurement. Two patients were recently diagnosed diabetics and only had one HbA1C result available which if taken within the previous month was not repeated and was considered as the "measured HbA1c". The first HbA1c measurements recorded (N=30) had a mean of 11,98% (SD: 3,73) whilst the more recent measured HbA1c measurements (N=34) had a mean of 12,24% (SD: 3,33). The time difference between the two measurements was a median of 1,44 years (IQR: 0,59-2,42) with a minimum difference of 2 months and a maximum difference of 11,6 years.

When grouped into categories 85,3% (29) had a measured HbA1c of >9,0% (see figure 3.1). The participants were receiving a mean of 0,82 units/kg (SD: 0,17) of insulin per day. A conventional regimen was prescribed for 50% (17) of patients. This consisted of two or less injections per day whilst 44,1 % (15) were prescribed an intensive regimen (3 or more injections per day). Two participants were receiving insulin (twice daily premixed insulin) and metformin, an oral hypoglycaemic agent. This was due to them having elevated BMI z scores of 3,64 and 3,16 respectively and features of insulin resistance. Glycosuria was found in 76,5% (26) of the cohort at the time of enrolment and 11,8% (4) had ketonuria but did not meet other criteria for diabetic ketoacidosis (DKA) and were not treated as such (see table 3.2).

When grouped by number of admissions, 73,5% (25) had been admitted ≤ 2 times since diagnosis, 20,6 % (7) had been admitted 3-5 times and 2 participants (5,88%) had been admitted more than 6 times. The reasons for admission were DKA (67,7%),

hypoglycaemia (11,7%), infection (5,9%) and hyperglycaemia (29,4%; see figure 3.2). One patient had a documented unrelated co morbidity namely Turners syndrome.

Table 3.2: Glycaemic control and insulin regimen in type 1 diabetic children and adolescents attending the CHBAH paediatric diabetic clinic

	n=34 (%)
Glycaemic control	
Mean (SD)[1] HGT[2] (mmol)	13,27 (6,37)
Mean (SD) 1st HbA1c[3](%)	11,98 (3,73)[4]
Mean (SD) Measured HbA1c (%)	12,24 (3,33)
Mean (SD) Insulin/Kg (units/kg)	0,82 (0,17)
Number of Admissions	
0-2 Admissions (%)	25 (73,5)
3-5 Admissions (%)	7 (20,6)
>6 Admissions (%)	2 (5,9)
Urine Dipstick[5]	
Proteinuria (%)	4 (11,8)
Glycosuria (%)	26 (76,5)
Ketonuria (%)	4 (11,8)
Haematuria (%)	2 (5,9)
Insulin regimen	
Conventional (%)	17 (50,0)
Intensive (%)	15 (44,1)
Other (insulin and metformin) (%)	2 (5,9)

[1]SD-standard deviation; [2]HGT-haemoglucose test; [3]HbA1c-glycosylated haemoglobin; [4]n=30; [5]Some participants had a combination of glycosuria and ketonuria/proteinuria/haematuria

Figure 3.1: HbA1c measurements in children and adolescents with IDDM attending the CHBAH paediatric diabetic clinic

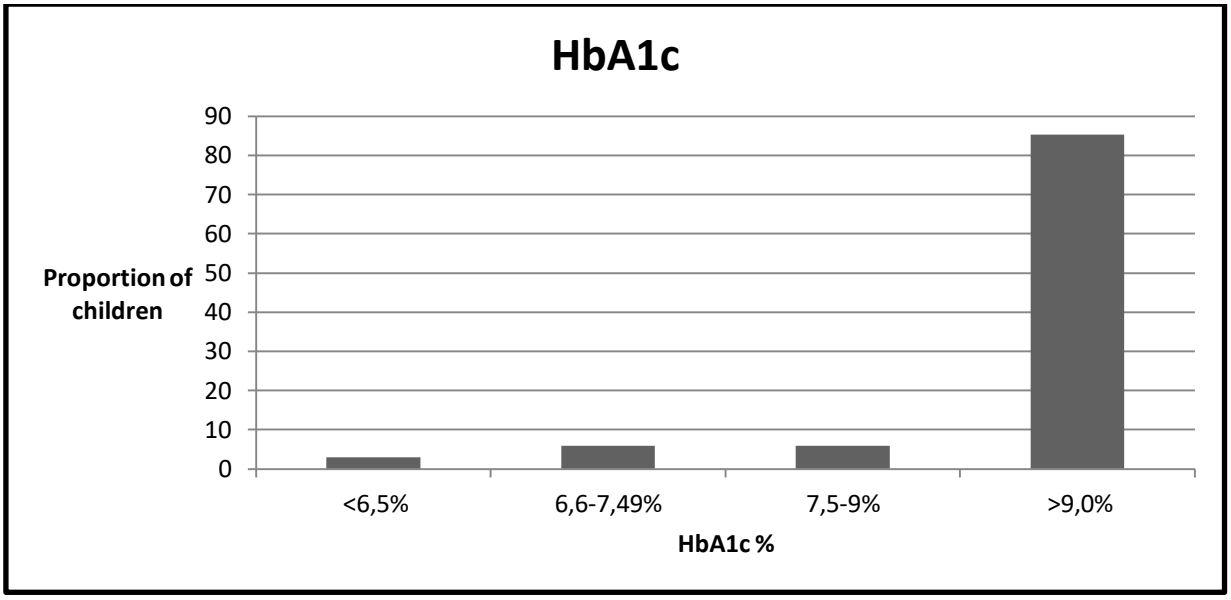
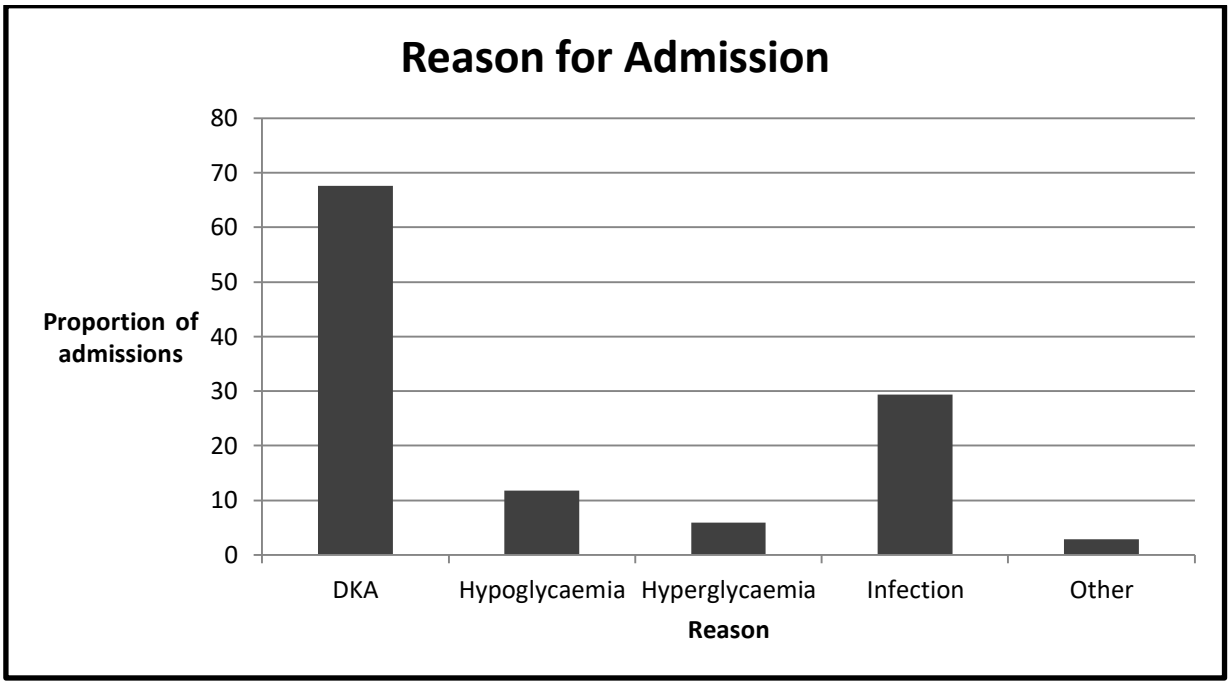


Figure 3.2: Reasons for hospital admissions in children and adolescents with IDDM attending the CHBAH paediatric diabetic clinic



3.2 Complications

Proteinuria was found in 11,8% (4) of participants and the median UACR was 0,5mg/mmol (IQR: 0,00-2,30), however only 32 results were obtained due the laboratory incorrectly processing two samples (see table 3.3). Only 18,7% (n=6) had a random UACR which was classified as being in the range of microalbuminuria. Only 1 out of the 6 participants who had microalbuminuria had confirmed diabetic nephropathy as mentioned above. The other 5 participants require further investigation to confirm the diagnosis. Because the study tested a single random urine specimen for ACR, the diagnosis of microalbuminuria was not confirmed in accordance with international guidelines. For this reason, associated risk factors could not be accurately analysed.

The results for renal function tests such as urea, creatinine and GFR showed normal values. One participant's blood tests were rejected by the laboratory due to insufficient blood being available for testing (n=33). The one participant with confirmed nephropathy had renal dysfunction reflected by a urea of 14,9mmol/l, creatinine 292umol/l and GFR 17,53ml/min/1,73m^2.

Most participants, 94% (32) were normotensive, whilst 2 participants (5,9%) were classified as "prehypertensive" according to the single measurement taken (see table3.3).

3.2.1 Diabetic Retinopathy

One participant had previously been diagnosed with bilateral cataracts (no retinopathy) and was being followed up by the ophthalmologists. No new changes in this participant were detected. There was a high rate of defaulted appointments as 9 (26,5 %) participants did not attend their scheduled retinal screening appointments. Of the remaining 24 participants that were screened, no retinal changes were detected (see table 3.3).

Table 3.3: Complications in type 1 diabetic children and adolescents attending the CHBAH paediatric diabetic clinic

	n=34 (%)
Retinopathy	
No Diabetic Retinopathy	24 (70,6)
Diabetic Retinopathy	0
Cataracts	1 (2,9)
Defaulted	9 (26,5)
Urine ACR	
Normal	26 (81,3)[1]
Abnormal	6 (18,7)[1]
Blood Pressure	
Normotension	32 (94,1)
Prehypertension	2 (5,9)
Hypertension	0
Renal Parameters	
Median (IQR[2]) urine ACR[3] (mg/mmol)	0,50 (0,00-2,30)[4]
Median (IQR) Urea (mmol/l)	3,50 (3,00-4,20)[5]
Median (IQR) Creatinine (umol/l)	49,00 (45,00-56,00)[5]
Median (IQR) GFR[6] (ml/min/1.73 m2)	104,70 (97,42-114,58)[5]

[1] n=32; [2] IQR-interquartile range; [3]ACR- albumin creatinine ratio; [4]n=32; [5]n=33; [6]GFR-glomerular filtration rate;

Although we were unable to accurately identify risk factors associated with microalbuminuria or retinopathy, the cohort was grouped by pubertal status, insulin regimen and duration of diabetes according to known associations. Race, gender, urine dipsticks, number and reasons for admission showed no significant difference in the comparative analysis (results not shown).

When pubertal and pre-pubertal participants were compared, there were significant differences in weight, height and age at interview (see table 3.4). There were no differences in measurements of other anthropometric parameters, demographic characteristics, glycaemic control or renal function. The pre-pubertal group was receiving

insulin at 0,84 units/kg (SD:0,14) and the pubertal group received insulin at 0,81 units/kg (SD:0,18) with no significant difference noted (p=0,59; see table 3.4).

Table 3.4: Comparison between pubertal and prepubertal participants: demographic, anthropometric and biochemical data of type 1 diabetic children and adolescents attending the CHBAH paediatric diabetic clinic

	Pubertal n=25	**Prepubertal n=9**	**P value**
Mean (SD)[1] Age At interview (years)	**12,46 (1,31)**	**10,57 (1,30)**	**≤0,01**
Mean (SD) Age At Diagnosis (years)	9,44 (3,31)	8,09 (2,72)	0,28
Median (IQR) [2] Duration Of Diabetes (years)	1,71 (0,53-5,22)	2,28 (1,01-3,22)	0,7
Anthropometry			
Median (IQR) Weight (kg)	**41,00 (37,00-44,60)**	**33,50 (28,40-36,30)**	**0,01**
Median (IQR) BMI[3] (kg/m^2)	18,26 (16,60-20,17)	17,20 (15,60-18,44)	0,43
Mean (SD) Height (cm)	**150,3(6,94)**	**135,94 (9,06)**	**≤0,01**
Mean (SD) Height/Age Z Score	-0,38(1,19)	-0,83 (1,40)	0,37
Mean (SD) BMI Z Score	0,19(1,34)	0,10 (1,19)	0,84
Weight/Age (percentile)	44,46(30,59)	34,11 (25,04)	0,37
Glycaemic control			
Mean (SD) HGT[4] (mmol)	13,72(6,23)	12,00 (6,97)	0,49
Mean (SD) 1st HbA1c[5] (%)	12,26(4,06)[6]	11,33 (2,91)	0,54
Mean (SD) Measured HbA1c (%)	12,53(3,34)	11,41 (3,35)	0,40
Mean (SD) Insulin/kg (units/kg)	0,81(0,18)	0,84 (0,14)	0,59
Renal Parameters			
Median (IQR) UACR[7] (mg/mmol)	0,90 (0,00-2,30)	0,30 (0,00-180) [8]	0,37
Median (IQR) Urea (mmol/l)	3,50 (2,85-3,95)[9]	3,80 (3,40-4,40)	0,26
Median (IQR) Creatinine (umo/l)	53,50 (45,50-6,00) [9]	46,00 (45,00-49,00)	0,07
Median (IQR) GFR[10] (ml/min/1.73 m^2)	102,52 (95,76-116,03[9])	107,12 (104,29-109,42)	0,67

[1]SD-standard deviation; [2]IQR-inter-quartile range; [3]BMI-body mass index; [4]HGT-haemoglucose test; [5]HbA1c-glycosylated haemoglobin; [6]n=21; [7]UACR-urine albumin creatinine ratio; [8]n=7; [9]n=24; [10]GFR-glomerular filtration rate

P values calculated using the Student's t test for parametric data and the Mann Whitney U test for non parametric data. Categorical data was analysed using the Fisher's exact test.

When grouped according to those participants receiving intensive or conventional insulin therapy, BMI and BMI z scores were found to be significantly different (see table 3.5). The two participants who were receiving metformin were not included in this analysis. The BMI in the conventional group was higher than in the intensive group with a median of 18,66 kg/m^2 (IQR: 17,20-20,05) vs. 17,00 kg/m^2 (IQR: 14,75-18,26; p=0,03). Similarly, the BMI z score was a higher 0,34 (SD: 0,86) in the conventional group compared to the intensive group -0,46 (SD:1,04; p=0,02). The weight for age percentile was a higher 48,29 in the conventional group (SD:23,80) compared to the intensive group which had a mean weight/age percentile of 26,55 (SD: 24,19; p=0,02). The insulin dosage between the conventional and intensive group remained similar despite being on different regimens (0,84IU/kg ± 0,16 and 0,83U/kg ± 0,16 respectively; see table 3.5).

Table 3.5: Comparison between participants receiving conventional vs intensive insulin regimens: demographic, anthropometric and biochemical data of type 1 diabetic children and adolescents attending the CHBAH paediatric diabetic clinic

Characteristics	Conventional	Intensive	
	n=17	n=15	P Value
Mean (SD[1]) Age At interview (years)	9,59 (2,86)	8,11 (3,46)	0,20
Mean (SD) Age At Diagnosis (years)	11,87 (1,440	11,89 (1,71)	0,97
Median (IQR[2]) Duration Of Diabetes (years)	1,25 (0,35-2,63)	2,39 (1,07-5,54)	0,10
Glycaemic Control			
Mean (SD) HGT[3] (mmol)	12,46 (6,40)	14,67 (6,63)	0,35
Mean (SD) 1st HbA1c[4] (%)	11,21 (3,68)[5]	12,33 (3,93)	0,44
Mean (SD) Measured HbA1c (%)	12,89 (3,97)	12,01 (2,19)	0,46
Mean (SD) Insulin/kg (units/kg)	0,84 (0,16)	0,83 (0,16)	0,90
Anthropometry			
Median (IQR) BMI[6] (kg/m^2)	**18,66 (17,20-20,05)**	**17,00 (14,75-18,26)**	**0,03**
Mean (SD) BMI Z Score	**0,34 (0,86)**	**-0,46 (1,04)**	**0,02**
Mean (SD) Height/Age Z Score	0,40 (0,61)	-0,68 (1,77)	0,54
Renal Parameters			
Median (IQR) UACR[7] (mg/mmol)	0,90 (0,02-2,30)[8]	0,30 (0,00-3,10)	0,69
Median (IQR) Urea (mmo/ll)	3,70 (3,00-4,40)	3,50 (2,80-3,80)[9]	0,45
Median (IQR) Creatinine (umo/ll)	49,00 (45,00-56,00)	48,50 (45,00-57,00)[9]	0,78
Median (IQR) GFR[10] (ml/min/1.73 m^2)	104,70 (98,07-115,04)	105,71 (95,42-111,24)[9]	0,71

[1]SD-standard deviation; [2]IQR-inter-quartile range; [3]HGT-haemoglucose test; [4]HbA1c-glycosylated haemoglobin; [5]n=13 (total (n) 1st HbA1c measurements were 30 however this analysis excludes 2 participants who received glucophage; [6]BMI-body mass index; [7]UACR-urine albumin creatinine ratio; [8]n=15; [9]n=14; [10]GFR-glomerular filtration rate. P values calculated using the Student's t test for parametric data and the Mann Whitney U test for non parametric data. Categorical data was analysed using the Fisher's exact test.

After removing the participant with Turners syndrome from the analysis, the same anthropometric measurements remained statistically significant between the conventional and intensive insulin therapy groups (data not shown).

The comparison between disease duration of more than 5 years and less than 5 years showed, as expected, a statistical significance for duration of diabetes and age at diagnosis (see table 3.6). Glomerular filtration rate also was significantly different with respect to disease duration (98,94 ml/min/1,73 m^2 and 109 ml/min/1,73 m^2 respectively; p=0,04). However all measurements except one, were in the normal reference range. The abnormal value was that of the participant with overt nephropathy, and when removed and the data was reanalysed, GFR no longer remained significantly different between the two groups (109,23 vs. 100,46 ml/min/1,73 m^2; p =0,09). There was no difference in indicators of glycaemic control, renal parameters or anthropometry between the two groups (see table 3.6).

Table 3.6: Comparison between participants with duration of diabetes more than 5 years or less than 5 years: demographic, anthropometric and biochemical data of type 1 diabetic children and adolescents attending the CHBAH paediatric diabetic clinic

	> 5 Years n=8	≤5 Years n=26	P
Mean (SD)[1] Age At Diagnosis (years)	**4,85 (2,54)**	**10,38 (2,02)**	**≤0,01**
Mean (SD) Age At Interview (years)	12,43 (2,08)	11,82 (1,35)	0,33
Median (IQR)[2] Duration Of Diabetes (years)	**5,86 (5,45-8,85)**	**1,16 (0,44-2,28)**	**≤0,01**
Glycaemic Control			
Mean (SD) HGT[3] (mmol)	15,65 (6,60)	12,53 (6,25)	0,23
Mean (SD) 1st HbA1c[4] (%)	11,58 (3,67)	12,13 (3,83)[5]	0,73
Mean (SD) Measured HbA1c (%)	12,95 (1,56)	12,02 (3,71)	0,50
Mean (SD) Insulin/kg (units/kg)	0,88 (0,13)	0,80 (0,17)	0,22
Anthropometry			
Mean (SD) BMI[6] Z Score	-0,01 (1,06)	0,22 (1,36)	0,67
Mean (SD) Ht/Age Z Score	-0,94 (1,69)	-0,36 (1,08)	0,25
Median (IQR) BMI (kg/m^2)	17,17 (16,64-19,67)	18,01 (16,58-20,05)	0,86
Mean (SD) Wt/Age (percentile)	30,95 (30,98)	45,03 (28,45)	0,24
Renal Parameters			
Median (IQR) UACR[7] (mg/mmol)	1,30 (0,00-13,60)	0,50 (0,00-2,10)[8]	0,68
Median (IQR) Urea (mmol/l)	3,70 (3,50-4,30)	3,50 (2,90-4,10)[9]	0,23
Median (IQR) Creatinine (umol/l)	55,50 (49,50-59,50)	48,00 (45,00-55,00)[9]	0,10
Median (IQR) GFR[10] (ml/min/1.73 m^2)	**98,94 (93,30-104,49)**	**109,23 (99,42-117,02)[9]**	**0,04**

[1]SD-standard deviation; [2]IQR-inter-quartile range; [3]HGT-haemoglucose test; [4]HbA1c-glycosylated haemoglobin; [5]n=22; [6]BMI-body mass index; [7]UACR-urine albumin creatinine ratio; [8]n=24; [9]n=25; [10]GFR-glomerular filtration rate;

P values calculated using the Student's t test for parametric data and the Mann Whitney U test for non parametric data. Categorical data was analysed using the Fisher's exact test.

4.0 Discussion

In this study, thirty four patients, aged 9-19 years, attending the CHBAH diabetic clinic were screened for the presence of nephropathy, retinopathy and their associated risk factors. Only one patient, with known long standing microvascular complications, undergoing treatment by nephrologists and ophthalmologists was identified to have both diabetic retinopathy and nephropathy. The remainder of the cohort showed no identifiable retinopathy and whilst five patients did have raised UACR values, we were unable to confirm nephropathy at this stage due to the limited duration of our study.

The predisposing factors for the development of retinopathy and nephropathy have been extensively studied. It is well accepted that age of onset, duration of disease, puberty, hypertension and poor glycaemic control play significantly influential roles in the development of microangiopathy. This cohort of participants was relatively young at diagnosis (9,90 years; SD: 3,19) and their duration of disease was short (1,88 years; SD: 3,19), when compared to other African and Western based studies which showed significant disease duration to be between five and ten years[3, 13, 16, 17, 35]. These findings are likely due to the established referral system, which allows for adolescent patients, who would have had longer disease duration, to be referred to the adolescent diabetic clinic managed by the adult physicians.

The short disease duration and young age of participants are factors likely responsible for the relative absence of complications detected at this point in time. Disease duration across all studies is implicated in the development of diabetic complications. However, in this cohort only 23,52% had a disease duration of more than five years. In keeping with most studies microvascular complications become clinically detectable only after at least 5 years of diabetes duration irrespective of glycaemic control.

The duration of disease, when statistically analysed, showed that GFR varied between patients with disease duration of more than 5 years compared to those less than five years (p=0,04). When the outlying case, a patient with biopsy confirmed nephropathy and abnormal values, was excluded from the analysis there was no longer a statistical significance. Therefore in the absence of other findings suggestive of nephropathy, the GFR in this study's cohort should not have been affected by the disease duration. This is supported by the fact that when this patient was removed from the analysis there was no longer a significant difference.

What is illustrated is that the single patient with overt nephropathy skewed the findings. As a case on its own, this patient had mean disease duration of 14,92 years, was 16 years at the time of the study and was in puberty. She also had been admitted multiple times with at least ten admissions in DKA. She was classified as "prehypertensive" according to her blood pressure reading but was in fact "hypertensive" on treatment. Despite being on an intensive insulin regimen (0,70IU/kg of insulin) her HbA1c level was 13,7%. She was prescribed a relatively low insulin dose in order to prevent recurrent episodes of documented hypoglycaemia which was thought to be a complication of diabetic gastropathy. She did not have classical diabetic retinopathy but she did have bilateral cataracts which had been surgically removed. This disease profile is in keeping with the known risk factors for nephropathy and retinopathy development.

The majority of the patients were pubertal (73,5%) suggesting that patients were diagnosed during puberty or just prior to the onset of puberty. However pubertal status in this study did not show significant influence on the glycaemic control, renal parameters or retinal signs. Despite the described increase in insulin requirements and relative insulin resistance that occurs during puberty, this group did not show a significantly higher insulin requirement when compared to the prepubertal group[27, 40].

Despite the metabolic abnormalities occurring in this chronic disease, appropriate growth was maintained in this cohort with overall growth parameters, BMI, height for age and weight for age, being normal according to standardised WHO and CDC parameters. The weights and heights in the pubertal group were, also as expected, higher than those in the prepubertal group, supporting the fact that appropriate growth was being achieved. Exceptions were one patient with Turner's syndrome and the previously mentioned patient with diabetic nephropathy and retinopathy, both of whom were significantly stunted.

A concerning finding was that the majority of patients (91,2%), all but five, had poor glycaemic control with HbA1c values greater than 7,5%. In fact the mean HbA1c was 12,95% (SD: 1,56) which according to ISPAD/IDF guidelines, places these patients at high risk for complications[69]. There was no clinically impressive improvement in their glycaemic control over time as the initial mean HbA1c did not decrease sufficiently with treatment over a median of 1,44 years. In fact, it increased from a mean of 11,98% (SD: 3,73) to a mean of 12,24% (SD: 3,33). This study did not explore factors contributing to glycaemic control and treatment adherence. In Western studies it has been shown that in a predominantly pubertal cohort, complex psychosocial issues play an influential role on glycaemic control[39]. The ISPAD guidelines mention endocrine changes, erratic meal and exercise patterns, poor adherence to treatment regimens, eating disorders and hazardous and risk-taking behaviour as significant contributors to difficulties in achieving glycaemic control in this age group.

Historically, it is known, that the patients who participated in this study have mainly financial, social and food security concerns which are likely to contribute the poor management of their condition. Our participants' poor glycaemic control is in keeping with the suggestion that African populations have poorer glycaemic control when compared to Western populations. Although this should translate into a higher prevalence of

microangiopathic complications, this was not reflected in this study's findings. The short duration of diabetes and small cohort are likely contributory factors.

The DCCT unequivocally concluded that an intensive insulin regimen, consisting of three or more injections per day (or continuous subcutaneous insulin infusion via an insulin pump), together with home glucose monitoring and lower blood glucose targets, improved glycaemic control and lowered the risk for developing micro and macrovascular complications[28, 29]. In our study 17 participants (50%) received conventional, twice daily injections of premixed fast and long acting insulin and 15 (44,1%) patients were on insulin regimens that included pre-meal rapid or ultra-rapid basal bolus insulin injections. Despite the different insulin regimens, the conventional group received a mean insulin dose of 0,84 IU/kg/day (±0,16) and the intensive group received 0,83 IU/kg/day (±0,14) of insulin. This was in keeping with the DCCT in which the insulin dose between the two groups was similar[28]. There was no difference in HbA1c measurements, random HGT's, frequency of glycosuria, urine ACR measurements or number of admissions between those patients receiving conventional or intensive regimens.

Growth parameters did differ between the two groups, with the conventional group having higher BMI values (18,66kg/m^2 vs.17kg/m^2; p=0,03), BMI Z scores (0,34 vs. -0,46; p=0,02) and weight for age percentiles (48,29 vs.26,55; p=0,02).

Insulin is an important regulator of both weight and height, albeit through different mechanisms. In a study conducted in 1993, changes in body weight, body composition, energy expenditure and fuel metabolism that accompany intensive insulin therapy were explored [82]. The study demonstrated that compliance to an intensive insulin regimen and dietary control produces a decrease in fasting plasma glucose, HbA1c and glycosuria[82]. This translated into an increase in weight gain due to increased fat mass. The increase in

mass was explained by an overall decrease in 24 hour energy expenditure due to a decrease in resting metabolic rate, and the reduction in glycosuria. The findings in our study showed the corollary but what is important to note is that there was also no difference in HbA1c, haemoglucose testing, or glycosuria between the intensive and conventional insulin regimen groups. This raises the suspicion that despite prescribing an intensive regimen, patient compliance to the insulin dosage and diabetic diet may not be optimal.

Our study demonstrated normal height parameters independent of insulin regimen. This occurred despite poor glycaemic control and a high frequency of glycosuria. Chronic diseases, specifically type 1 diabetes, negatively affects linear growth velocity and pubertal changes. The GH-IGF axis, in which insulin is an important mediator, plays a pivotal role in linear bone growth. In an untreated diabetic state, low hepatic portal vein insulin levels occur. This induces GH hyper -secretion, low circulating levels of IGF-1 and low levels of IGF binding protein 3 (IGFBP). Simultaneously high levels of the counter-regulatory hormone, IGFBP-1 are induced. It is this mechanism which is responsible for growth retardation in children with IDDM[83]. Studies show that intensive insulin therapy prevents this physiological derangement responsible for stunted growth and may allow for normal height achievement in children with diabetes[83]. Our study showed that both conventional and intensive insulin therapy allowed for normal growth velocity, taking into consideration that both regimens provided a similar daily insulin dose.

One of the biggest limitations of this study involved participant follow up at the St John Eye Hospital for retinal screening. Only 24 out of 34 participants attended their ophthalmology screening appointments, with one participant already known to the ophthalmology department. No retinal changes were detected in those who were examined. Again the short duration of diabetes in a relatively young cohort seems to be in keeping with no findings of retinopathy in this cohort.

Although dilated indirect ophthalmoscopy is an accepted screening method for detecting diabetic retinopathy, the gold standard is 30 degree stereoscopic photography of seven standard fields on colour film[56]. The technical and financial costs of this screening method make it impractical in our setting. No retinopathy was detected in our cohort using indirect ophthalmoscopy. However, results may have been affected by inter-observer variability and the lower sensitivity of this method. Although most retinal examinations were performed by the paediatric ophthalmology consultant, the unpredictable environment and high patient load at the St John Eye Hospital required that some patients be seen by other ophthalmologists with different levels of expertise and training.

The most noteworthy limitation of this study was the small sample size and cross sectional study design. Due to the low prevalence of childhood diabetes in South Africa, a longitudinal evaluation of this cohort would have been a better study design. This was originally proposed in the protocol but the expected study duration would have been too long, given the limited time capacity.

The cohort demonstrated a narrow age range with a short duration of diabetes. Prolonged disease duration is associated with a high likelihood of developing complications. A cohort of children displaying a wider age range, and longer disease duration would have been a more optimal study population for identifying microvascular complications and associated risk factors.

Other limitations of this study included the limited time for urine screening. Since patients were seen only once, repeated urine specimens were not collected for those whose UACR were in the range of microalbuminuria. This prevented the definitive diagnosis of diabetic nephropathy at this time. Although analysis of multiple screening samples, over a six month period, was intended, the limited time available for this Master's research report

prevented this from being implemented. The urine specimens were collected randomly which increased the likelihood of false positive results in the sample.

A sometimes unreliable laboratory service resulted in several specimens being rejected, or processed using the wrong tests. This accounted for one blood specimen and two urine specimens being rejected/not measured. Results were also not available for baseline HbA1c's in two patients. Reasons for this may involve the inconsistent health care attendance by patients and the fact that patients are not always seen by the same doctor at each visit.

5.0 Conclusions and Recommendations

The development of diabetic retinopathy and nephropathy is well described to be associated with glycaemic control, age of onset and duration of diabetes, puberty and hypertension. International guidelines over the last several years have modified their recommendations with trends tending towards tighter glycaemic control and more practical and cost effective timing and methods of screening for nephropathy and retinopathy. ISPAD and ADA now recommend HbA1c targets of less than 7,5 % whilst the NICE guidelines recommend targets below 6,5%[59, 84]. Screening for retinopathy and nephropathy according to ISPAD/IDF, ADA and NICE should be done from 10 to 12 years of age or at the onset of puberty, with the duration of diabetes between two to five years[1, 57, 59]. The Canadian Diabetes Association currently recommends even later screening from 12-15 years with disease duration of more than 5 years[58]. Ongoing screening in accordance with international guidelines is particularly pertinent in this study's cohort, given their poor glycaemic control.

Despite the poor glycaemic control in this study cohort, the duration of disease was short and as such no new retinopathy was detected and no new nephropathy was confirmed. Since evidence has shown that glycaemic control is a significant contributing factor to the development of microvascular complications in diabetes mellitus, it would be advisable that future studies address contributing factors and potential solutions.

Although the study has limitations, its findings are in keeping with current guidelines advocating that screening should be done after 5 years of diabetes duration. With time, this group of diabetic children is at continued risk for development of such complications and close monitoring will be required to implement appropriate management.

Recommendations for future studies would be to clarify the difficulties in achieving euglycaemia in this population and the reasons for poor compliance. Subsequent interventions designed to overcome these challenges should be evaluated, in the hope of improving diabetic control and decreasing the progression to microvascular and macrovascular target organ damage. Social dynamics such as patient and caregivers' socioeconomic status, food security, educational status and home language in relation to that of the health care providers should be explored. Access to health care, the understanding of disease itself, attitudes to western medicine and the practical implication of a "healthy lifestyle" should be evaluated. Patient related factors such as difficulties in complying with the prescribed insulin regimen, undesired side effects, the stigma of chronic disease and the perceived lifestyle limitations should be considered, in order to facilitate holistic health care, for high risk patients.

In addition, a longitudinal study including older adolescents would be recommended in order to definitively assess microvascular complications, monitor indicators of glycaemic control and evaluate overall child health and growth.

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Appendix 1

Tanner stages of puberty[74]

Genitals (male)

Tanner Stage	
I	• Testicular volume less than 1,5 ml • Small penis of 3 cm or less (prepubertal) • < 9 years
II	• Testicular volume between 1,6 and 6 ml • Skin on scrotum thins, reddens and enlarges • Penis length unchanged • 9–11 years
III	• Testicular volume between 6 and 12 ml • Scrotum enlarges further • Penis begins to lengthen to about 6 cm • 11–12,5 years
IV	• Testicular volume between 12 and 20 ml • Scrotum enlarges further and darkens • Penis increases in length to 10 cm • 12,5–14 years
V	• Testicular volume greater than 20 ml • Adult scrotum and penis of 15 cm in length • >14 years

Breasts (female)

Tanner Stage	
I	• No glandular tissue • Areola follows the skin contours of the chest (prepubertal) • < 10 years
II	• Breast bud forms, with small area of surrounding glandular tissue • Areola begins to widen • 10–11,5 years
III	• Breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast • 11,5–13 years
IV	• Increased breast size and elevation • Areola and papilla form a secondary mound projecting from the contour of the surrounding breast • 13–15 years
V	• Breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla • >15 years

Pubic hair (both male and female)

Tanner Stage	
I	• No pubic hair at all (pre-pubertal) • < 10 years
II	• Small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum (males) or on the labia majora (females) • 10–11,5 years
III	• Hair becomes more coarse and curly, and begins to extend laterally • 11,5–13 years
IV	• Adult–like hair quality, extending across pubis but sparing medial thighs • 13–15 years
V	• Hair extends to medial surface of the thighs • >15 years

Appendix 2

R14/49 Dr Sarah Berkenfeld

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150303

NAME: (Principal Investigator)	Dr Sarah Berkenfeld
DEPARTMENT:	Paediatric Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Diabetic Microvascular Complications in Type 1 Diabetic Children and Adolescents Attending the Chris Hani Baragwanath Academic Hospital Paediatric Diabetic Clinic
DATE CONSIDERED:	27/03/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr FY Moosa
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	11/05/2015

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 Secretary in Room 10004, 10th floor, Senate House, University

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.**

Berkenfeld
Principal Investigator Signature

31/4/2015
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 3

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Sarah Berkenfeld

Student Number: 0310324F

This research report is submitted in partial fulfilment of the requirements for the degree of Master of Medicine in the Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Witwatersrand, Johannesburg

Johannesburg, 2016

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