Out of the
Department of Internal Medicine II - Grosshadern,
Ludwig-Maximilians-Universität, Munich

Determinants of outcome of children with type 1 diabetes in the North West Region of Cameroon

Doctoral Thesis
for the awarding of a Doctor of Philosophy (Ph.D.)
at the Medical Faculty of
Ludwig-Maximilians-Universität, Munich

submitted by

Loveline Lum Niba

born in

Bafut-Mezam, Cameroon

submitted on

26.04.2016

Supervisors LMU:

Habilitated Supervisor	Prof. Dr. med. Klaus G. Parhofer
Direct Supervisor	Dr. med. Benedikt Aulinger
3rd LMU Supervisor	
4th LMU Supervisor	

Supervisor External:

Local Supervisor	Prof. Wilfred F. Mbacham

Reviewing Experts:

1st Reviewer	Prof. Dr. med. Klaus G. Parhofer
2nd Reviewer	Dr. med. Benedikt Aulinger

Dean: Prof. Dr. med. dent. Reinhard Hickel

Date of Oral Defense: 21.11. 2016

Affidavit

Loveline Lum Niba

Name

Catholic University of Cameroon (CATUC), Bamenda

Street

P.O. Box 782, Bamenda

Zip code, town

Cameroon

Country

I hereby declare, that the submitted thesis entitled

Determinants of outcome of children with type 1 diabetes in the North West Region of Cameroon

is the result of my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

The submitted thesis or parts thereof have not been presented as part of an examination degree to any other university.

I further declare that the electronic version of the submitted thesis is congruent with the printed version both in content and format.

Bamenda, 26.04.2016

Place, Date

Signature of PhD Candidate

KEYWORDS:
Predictors, glucose control, HbA1c, type 1 diabetes, children/adolescents.

ABSTRACT

Background: In sub-Saharan Africa the prognosis of children with type 1 diabetes is poor. Many are not diagnosed and those that are diagnosed have a reduced life expectancy (less than one year). This study set out to identify the factors that predict glucose control in children and adolescents with type 1 diabetes in the North West Region of Cameroon.

Methods: A hospital based cross-sectional study involving 76 children/adolescents (41 girls and 35 boys, mean age of 15.1 ± 3.1 years) suffering from type 1 diabetes included in the "Changing Diabetes in Children" (CDiC) program and attending the clinics for children living with type 1 diabetes in the North West Region. Data on glycosylated haemoglobin (HbA1c) as well as clinical and biochemical parameters at diagnosis and during the study period were obtained from the hospital records of participants. A structured questionnaire was used to obtain information on socio-demographic characteristics and diabetes related practices from participants. Odds ratios (OR) were calculated using logistic regression to assess the association between determinants and good glucose control.

Results: The study population had a mean HbA1c of 10.3 ± 2.9%. There was a significant decrease in the mean HbA1c from diagnosis (11.1%) to the study period (10.3%) (p = 0.011). Multivariate analysis indicated that having a mother as the primary caregiver (OR 0.02, 95% CI 0.002 – 0.189) and minimal/moderate caregiver involvement in insulin injection (OR 26.8, 95% CI 4.4 – 56.1) were independent predictors of glucose control.

Conclusion: This study has demonstrated that having a mother as a primary caregiver is an important predictor of good glycaemic control among children with type 1 diabetes. It is currently unclear whether the direct involvement of the mother is important or whether "mother as a primary caregiver" is a strong indicator for a setting in which diabetes treatment is possible.

TABLE OF CONTENT

I. LIST OF FIGURES

II. LIST OF TABLES

III. ABBREVIATIONS

ADA	American Diabetes Association
T1DM	Type 1 diabetes mellitus
T1D	Type 1 diabetes
T2DM	Type 2 diabetes mellitus
T2D	Type 2 diabetes
HbA1c	Glycosylated haemoglobin
WHO	World Health Organization
IDF	International Diabetes Federation
ISPAD	International Society for Pediatric and Adolescent Diabetes
CDiC	Changing Diabetes in Children
DCCT	Diabetes Control and Complications Trial
EDIC	Epidemiology of Diabetes Interventions and Complications
GADA	Glutamic acid decarboxylase autoantibodies
IAA	Insulin autoantibodies
ICA	Islet cytoplasmic autoantibodies
IA2A	Tyrosine phosphatase islet antigen 2 autoantibodies
UK	United Kingdom
USA	United States of America
BGM	Blood glucose monitoring
SES	Socioeconomic status
DKA	Diabetic ketoacidosis
BMI	Body mass index
CI	Confidence interval
ANOVA	Analysis of variance
OR	Odds ratio
HLA	Human leucocyte antigens
GDM	Gestational diabetes mellitus
MODY	Maturity onset diabetes of the young
OGGT	Oral glucose tolerance test

FPG	Fasting plasma glucose
NGSP	National Glycoheamoglobin Standardization Program
LDL-C	Low density lipoproteins- cholesterol
SDS	Standard deviation score
BP	Blood pressure
SBP	Systolic blood pressure
DBP	Diastolic blood pressure

1. INTRODUCTION.

1.1. Definition and classification of diabetes.

Diabetes mellitus is a group of complex multifactorial metabolic disorders which is characterized mainly by hyperglycaemia resulting from defects in the action of insulin and/or the secretion of insulin[1]. The development of diabetes usually involves many pathogenic processes which may range from organ-specific autoimmune destruction of pancreatic beta (β) cells which are responsible for insulin secretion, characterized histologically by inflammation of islet cells[2] and consequently abnormalities resulting in resistance to insulin[1]. The elevated plasma glucose is associated with chronic complications such as cardiovascular diseases, kidney disease, peripheral neuropathy with risk of foot ulcers and blindness[1]. Moreover, diabetes mellitus is currently a growing public health burden to the individual, the family and the society and its rates worldwide have reached alarming proportions[3].

Currently, diabetes is classified into four subtypes based on the etiology of the disease (Table 1). These include type 2 diabetes mellitus (T2D), type 1 diabetes mellitus (T1D), gestational diabetes as well as drug or chemically induced diabetes. This classification suggest that hyperglycaemia can be subcategorized into those that require insulin for survival, those requiring insulin for control (i.e. for metabolic control and not for survival) and those not requiring insulin (i.e. non-pharmacological treatment methods or treatment with drugs other than insulin)[1,4].

Table 1.1: Etiologic classification of diabetes mellitus based on the position statement of the American Diabetes Association (ADA).[1]

I	Type 1 diabetes (destruction of β cell, usually associated with absolute insulin deficiency) • Immune mediated diabetes (Type 1A) • Idiopathic diabetes (Type 1B)
II	Type 2 diabetes (resistance to insulin with relative insulin deficiency and/or a defect of insulin secretion associated with insulin resistance)
III	Other specific types: A. Genetic defects of beta (β) cell function (e.g. MODY) B. Genetic defects in the action of insulin C. Exocrine pancreas diseases (e.g. pancreatitis) D. Endocrinopathies (e.g. Cushing's syndrome, hyperthyroidism) E. Drug or chemical-induced (e.g. glucocorticoids, thyroid hormone) F. Infections (e.g. congenital rubella) G. Rare forms of immune-mediated diabetes (antibodies against insulin receptors) H. Other genetic syndromes associated with diabetes (e.g. Turner syndrome)
IV	Gestational diabetes

MODY: Maturity onset diabetes of the young
Source: American Diabetes Association[1].

1.1.1. Type 2 diabetes.

Type 2 diabetes accounts for about 15% to 45% of all the newly diagnosed cases of diabetes in children and adolescents[5], and 90% – 95% of all the cases of diabetes and it is as a result of a change in the balance between insulin secretion and sensitivity of insulin[1]. However, a study by Neu *et al.*[6] reported that in German children type 2 diabetes is rare and that it was also the case in other European countries. Type 2 diabetes is most often characterized by insulin resistance with the individuals involved usually having a relative but not complete

insulin deficiency[1]. Also, the disease is very heterogeneous with respect to its genetic, metabolic as well as clinical characteristics.

Type 2 diabetes incidence in children and adolescents has increased dramatically in some ethnic groups and countries since the 1990s. This has been attributed to increase in urbanization rates, economic development and this rise is mirroring increasing rates in overweight and obesity although the genetic predisposition of some ethnic populations might also be responsible for the rise[7]. For instance, a study by Pinhas-Hamiel and Zeitler[5] found that about 80% of all new cases of pediatric diabetes in Japan are type 2. On the contrary in the UK, among children less than 17 years type 2 diabetes was less common with a minimum incidence of 0.53 per 100,000 children/year observed[8]. Finally, type 2 diabetes is frequently linked with obesity[1,7] (predominantly fat distribution around the abdomen) and lack of physical activity and it is also characterized by older age of onset.

1.1.2. Type 1 diabetes (T1D).

Type 1 diabetes is the most common form of diabetes in childhood and it is characterized by deficiency in insulin resulting from the autoimmune destruction of pancreatic β-cells[9, 10,11], in genetically susceptible individuals. It accounts for about 5% – 10% of all the cases of diabetes with a majority of the patients (approximately 40%) diagnosed before the age of 20[12,13]. Impairment in the secretion of insulin and deficiency in the action of insulin is usually the main cause of the elevated blood sugar in individuals with type 1 diabetes. Polyuria, weight loss, polydipsia and blurred vision are most often the consequences of the elevated plasma glucose levels. Also, susceptibility to certain infections and growth retardation may also be associated with the very high blood sugar[14].

Etiologically, type 1 diabetes might be subdivided into two groups which include; autoimmune (immune-mediated) and idiopathic. The autoimmune group (type 1A) is polygenic, accounts for about 80% – 90% of all T1D cases and it is the most frequent type of the disease whereas, type 1B also known as idiopathic, presents with all the clinical features of the autoimmune group except for the autoimmune aspect[15].

Type 1 diabetes is also the form of diabetes that requires life insulin therapy, but the metabolic characteristics vary considerably, both before and at diagnosis[16]. Moreover, autoantibodies associated to diabetes are not always sufficient to define a categorical disease phenotype since patients who evolve to insulin requirement are usually characterized by both autoantibodies and younger age at diagnosis, little endogenous secretion of insulin, lower body mass index and high levels of glycosylated haemoglobin (HbA1c) at the time of diagnosis (Figure 1.1). Therefore, juvenile-onset of T1D is the most genetically determined and most severe form of the disease.

Further, T1D has traditionally been considered a disease of childhood and early adulthood. However, recent data suggest that only about 50% – 60% of those with type 1 diabetes are less than 18 years at presentation and that the disease also occurs throughout adulthood but the incidence level is low[17].

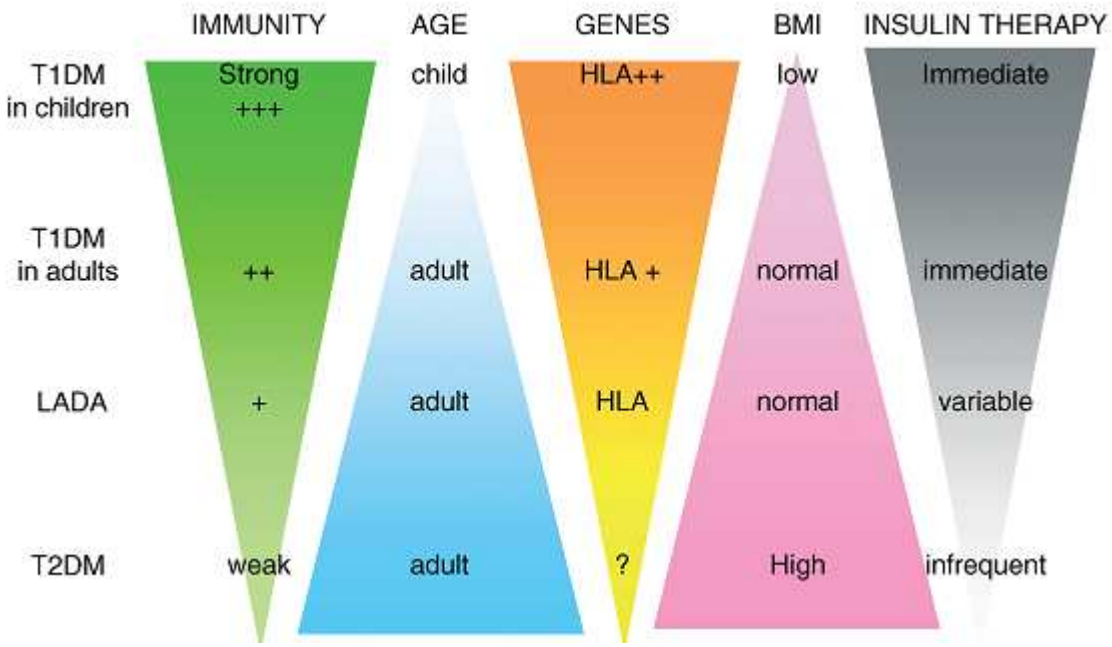

Figure 1.1: The range of diabetes covers variable risk according to the type of diabetes for immune changes, the age at presentation, obesity (assessed by body mass index), HLA genetic susceptibility and treatment with insulin (Figure and legend from Leslie *et al.* 2008)[16].

1.1.3. Pathophysiology of type 1 diabetes.

The deficiency of insulin in T1D may be seen as a result of the beta (β) cell damage within the pancreas resulting in autoimmunity in individuals who are genetically susceptible[2]. The β-cells are glucose automatic regulators, which control the release of insulin to maintain physiological glucose levels[10]. The process of producing antibodies against islet cells as a result of this process is a marker of the onset of an autoimmune disease activated by autoreactive T cells. These T cells which are capable of destroying β cells result in a gradual loss in its insulin secretory function[9].

Given that clinical T1D (i.e. presence of symptoms) does not present until about 80% to 90% of the β cells have been destroyed, there is a noticeable gap between the onset of autoimmunity and the onset of diabetes (Figure 1.2). A recent study by Atkinson[9] suggest that 40% to 50% of β cells are viable at the onset of hyperglycemia and this might be the reason why the secretion of insulin may remain stable for long periods in persons with T1D despite the production of autoantibodies. A loss of first-phase insulin response (as measured by intravenous glucose tolerance) is generally followed by a period of intolerance to glucose and also a period of clinically 'silent' diabetes[18] which usually occurs when the regenerative capabilities of the beta cells is overwhelmed by autoimmunity.

Several studies have identified a series of autoantigens as markers for autoimmunity in patients with T1D including autoantibodies to insulin (IAA), islet cytoplasmic autoantibodies (ICA), autoantibodies to the 65-kD form of glutamic acid decarboxylase (GADA)[19], tyrosine phosphatase-related islet antigen 2 (IA-2)[20] as well as autoantibodies against the zinc transporter ZnT8 (Slc30A8) [21]. Even though a study by von Herrath *et al.*[22] suggested that there may be three or more antigens at the beginning of the process of autoimmunity against pancreatic beta cells, the authors concluded there is no consensus on the exact nature and immunological process associated with the primary autoantigen that occurs in T1D, as many antigens are involved in activating the process at the end.

A study in Cameroon by Hawa *et al.*[23] to evaluate the presence of autoantibodies in 47 patients with type 1 diabetes reported that 34% and 6.4% had GAD and IA2 autoantibodies respectively. Nevertheless, this study was carried out in adult type 1 diabetic patients and the

findings may not reflect the situation among children and adolescents with type 1 diabetes. In another study in Tanzania by Lutale *et al.*[24] to assess the occurrence of autoimmune mediated type 1 diabetes, the authors found that 29.8% of the patients had GADA and 21.3% had IA-2A and the frequencies of these pancreatic autoantibodies was lower than that observed in Caucasian populations. Also, the overall prevalence of islet cell antibodies (ICA) was reported to be 42.6% among patients with T1D compared to 7.3% among type 2 diabetic patients. The authors attributed the significant presence of autoantibodies in most type 1 diabetic patients with a positive family history of diabetes. In addition, a study from Tunisia among newly diagnosed children with type 1 diabetes found a higher prevalence of autoimmune markers with 90.7% of the children having at least one autoantibody[25]. In this study 57% of the patients were positive for islet cell antibodies (ICA), 65.1% had GADA, 43% had IA-2A and 50% had IAA. This is an indication that most of the cases of type 1 diabetes in African children may be considered as immune mediated.

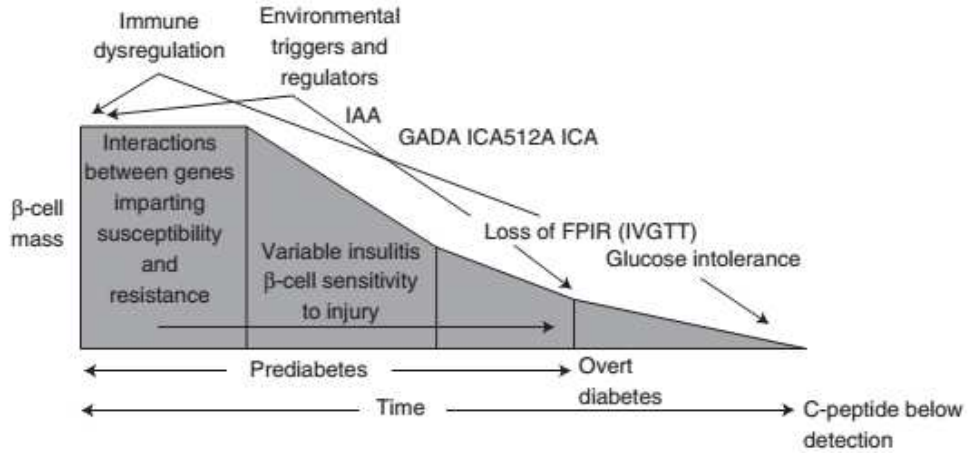

Figure 1.2: Model of type 1 diabetes natural history and pathogenesis. This model expands on the traditional model by including information which has been gained through an improved understanding of the roles for immunology, genetics and environment in the natural history of T1D (Figure and legend from Atkinson, 2012) [9] .

Research has been able to identify the contribution of genetics to the risk of the disease and among all the genes which have been linked with type 1 diabetes, the human leucocyte antigen (HLA) was found to have the strongest association[26]. T1D does not conform to any of the simple inheritance patterns in spite of the obvious effect of genetic factors, as such it

is still considered a complex and multigenetic disorder[26]. In addition, studies have confirmed the effect of genetics and the environment in type 1 diabetes. For instance, the risk of type 1 diabetes was 1 in 20 for an individual in the United States (US) having a first degree relative with T1D, whereas the general population had a 1 in 300 risk[27]. Again, studies on monozygotic twins have shown the risk to be between 30% – 50%, meanwhile, dizygotic twins had a concordance of 6% – 10%[28].

1.1.4. Environmental risk factors for type 1 diabetes.

Evidence has implicated the role of exogenous factors in the development of T1D as triggers and enhancers of β-cell destruction[29,30]. Studies among monozygotic twins have found a pairwise concordance of < 40%[31,32], implying that there is either an acquired postconceptional genetic discordance or the role of non-genetically determined factors. Also, studies have reported that of all the individuals with the HLA diabetes susceptibility genes, less than 10% develop the clinical disease[33,34], and this may be explained by the powerful influence of one or more environmental triggers. In addition, a steep global rise in the incidence of T1D in childhood in the last five decades, most especially in Europe[35] with a more than ten-fold difference in disease incidence has been reported among children below 15 years of age living in Europe[36]. This cannot exclusively be due to the increased genetic disease susceptibility in the population but most likely reflect changes in lifestyle and the environment. Moreover, data on migrant studies from population groups who have moved from low-incidence to high-incidence regions indicate an increase in T1D incidence, underscoring the influence of exogenous factors[37].

The exact mechanism responsible for the process leading to autoimmunity remains unknown[38]. However, putative triggers including infectious agents (e.g. enteroviruses, coxsackie, congenital rubella) or components of early diet (cow milk protein, cereal or gluten exposure)[39,40], are thought to initiate the process of autoimmunity, leading to extensive β cell destruction and ultimately clinical manifestation of type 1 diabetes. Also, environmental factors playing a role in the pathogenesis of T1D may differ substantially from population to population given different exposures to a given risk factor or because of the genetic susceptibilities of populations to the risk factor[41]. These may include perinatal

factors[42,43], increased weight gain during infancy[44,45], exposure to sunlight and vitamin D sufficiency[46,47] and dietary factors[48] .

In addition, Cardwell *et al.*[49] in a meta-analysis demonstrated that children from caesarean section delivery have an increased risk of childhood type 1 diabetes. Given the disproportional influences of maternal factors on the risk of T1D is suggestive of critical disease-inducing environmental events that operate very early in life (even in the uterus) and these maternal-related events are associated with an increased risk of the disease in children which is not the case in adults[50].

Maternal habits during pregnancy.

Maternal habits during pregnancy such as tea drinking and smoking have been shown to be associated with an increased risk for type 1 diabetes in their children[41,51]. For instance, Majeed and Hassan[51], in a study in Basrah realized that the drinking of tea, exposure to environmental risk factors (pre-eclampsia, and infectious diseases) during pregnancy and neonatal period (jaundice and infections) in early infancy were significantly associated with the development of type 1 diabetes. Also, a study in Italy reported similar findings[41]. Another Swedish study also reported that maternal smoking (> 9 cigarettes a day) in early pregnancy was associated with a higher risk (OR 3.91) of the child developing type 1 diabetes[52].

Maternal age at delivery.

Maternal age at delivery has been found to be a high risk factor of T1D in their offspring with the risk being highest in firstborns[53]. However, evidence on the role of maternal and neonatal factors in the development of childhood T1D is inconclusive. While several studies have found a significant association between increased maternal age with an increased risk of type 1 diabetes [43,54], others have not found any association[55,56].

Breastfeeding.

Breastfeeding has been proven to have a protective effect against T1D while cow milk increases the risk of developing type 1 diabetes[34,57]. A previous study found concomitant

diseases and early infant nutrition to be some of the environmental risk factors associated with the development of childhood type 1 diabetes[48]. For example, a study by Visalli *et al.*[41] in Italy on genetically susceptible T1D individuals found that breast feeding for less than three months and the presence of eczema were risk factors for T1D in this Southern European population. Also, early weaning, and suspension of breast feeding for cow milk formula before 3 months of life were all higher for type 1 diabetics than for non-diabetics in the same study.

Birth weight.

A previous study suggests that birth weight and weight gained during infancy or the first year of life are associated with an increased risk of developing T1D later in life[58]. Also, a study in South Iran has shown that increased birth weight (≥ 4kg) is a potential risk factor for type 1 diabetes (OR 2.04)[59], while in a meta-analysis by Harder *et al.*[60], low birth weight (< 2,5kg) was associated with a decreased risk of type 1 diabetes. The authors reported that every 1 kg increase in birth weight was associated with a 7% increase risk of developing type 1 diabetes.

1.2. Global situation of type 1 diabetes mellitus.

1.2.1. Incidence and prevalence of type 1 diabetes mellitus from a global perspective.

Despite tremendous progress by developed nations to improve access to diabetes care and adequate management of the disease, type 1 diabetes remains a growing public health concern given the upturn in incidence, a trend that is currently observed worldwide[14,61]. This present situation has been described as the most challenging health problem of the 21st century[62], with an estimated 542,000 children (under the age of 15) worldwide living with type 1 diabetes and 86,000 developing type 1 diabetes annually[14].

Like the rest of the world, sub-Saharan Africa is not exempted from diabetes and the increasing number of families affected remains a challenge[63,64]. Also, over the past decades, diabetes has emerged as a major health challenge in the region[65,66], where an estimated 14.2 million adults aged 20 – 79 years are now estimated to have type 2 diabetes and 46,400 children (below the age of 14) are suffering from type 1 diabetes[14]. Notwithstanding, T1D

among children in sub-Saharan Africa has a high rate of mortality and less than half of these children are diagnosed[64]. What is more daunting is the fact that compared to countries in the developed world, children diagnosed in developing countries have a reduced life expectancy (less than one year)[64,67].

Large international collaborative studies such as the Diabetes Mondiale study (DIAMOND) [68], the Europe and Diabetes study (EURODIAB) [69] and the SEARCH for diabetes in youth study[70], during the last decades have offered significant contributions to global trends in the incidence and epidemiology of the disease. These studies have reported an upward trend in the incidence of T1D among children under the age of 15 years in many countries with an overall annual increase estimated at 3%[68,69]. Nonetheless, a large geographical variability in the incidence rates of childhood type 1 diabetes have been reported[71]. In Western countries, the prevalence has been found to be higher compared to the African region partly due to higher surveillance and diagnostic rates in the developed world compared to Africa.
In 2015, according to the International Diabetes Federation (IDF) Diabetes Atlas[14], of the estimated 542,000 children living with type 1 diabetes, 46,400 were estimated to be living in Africa alone with 7,600 children newly diagnosed annually. In addition, 26% of the newly diagnosed children globally came from Europe and 22% from the Caribbean and North America[14].

Table 1.2: Global estimates of type 1 diabetes in children (< 15 years).

Parameter	**2015**
Child population	1.9 billion
Number of children with type 1 diabetes	542,000
Number of new type 1 diabetes cases per year	86,000
Annual increase in incidence	3%*

Source: Diabetes Atlas 7th edition International Diabetes Federation, 2015.
*Estimates from the *Diabetes Mondiale study* (DIAMOND) [68], the *Europe and Diabetes study* (EURODIAB) [69]

According to data from the DIAMOND study there was a 350-fold variability in incidence levels across the studied populations between 1990 and 1999. In Europe, the annual

incidence in most countries from 1989 to 2003 was found to be increasing with an overall annual increase of 3.9%[69]. Finland had the highest incidence (40 cases per 100,000 children at risk) of type 1 diabetes worldwide, whereas the lowest incidence (0.1 cases per 100,000 children per year) was reported in the Zunyi region in China[68,72]. These studies also described large intercontinental variation in incidence rates.

In the USA, the estimated prevalence of diabetes in 2009 (both T1D and T2D) in people younger than 20 years was 0.22%[73], implying that 1 in every 433 persons less than 20 years had diabetes. Also, an annual prevalence for type 1 diabetes was estimated at 1.93 per 1,000 in children less than 20 years in 2009[73]. Among South American populations, the incidence varied between very low to high (2-10 per 100,000/year), whereas in Central America the variation ranged from 1.5 to 17/100,000/year.

Europe is a region with the most informative and reliable data on incidence where a north to south gradient has been described, varying from the highest in Finland (43.9/100,000/year) and some of the other Scandinavian countries to the lowest being reported in Macedonia (3.2/100,000/year)[36,74,75].
A study in the Karnataka region of India, reported an annual incidence of 0.32/100,000 per year based on a diabetes registry from 1995 to 2008[76].

There are only a few African studies in the literature that have reported the incidence and prevalence of T1D. Most of the studies are hospital-based as opposed to population based studies conducted about two to three decades ago; therefore the true population prevalence remains unknown. As a result of scarcity of data in the African continent, the region's contribution to global estimate of type 1 diabetes incidence is low. However, in children less than 14 years in the African region, an incidence estimate of 6.4/100,000 per year of new cases of T1D has been reported[77]. The high childhood mortality rates in the African continent may contribute to the low ascertainment of cases in countries where incidence data does exist. For instance, studies from North Africa have shown that the incidence varies, ranging from 4.4/100,000 in Algeria[78] to 20/100,000 in Morocco[79]. Moreover, only Sudan

and Tanzania in sub-Saharan Africa have data on T1D incidence. Incidence estimates from Sudan, indicated that the incidence increased from 9.5/100,000 to 10.3/100,000 in 1991 and 1995 respectively[80,81]. In addition, an incidence of 1.5/100,000 per year was estimated for Tanzania[82]. However, the data used in this study was from 1991 and follow up studies have not yet been carried out.

Of particular concern is the rising incidence of type 1 diabetes in the youngest age group, affecting mostly the poor and posing a threat to the fragile health systems in most low income countries. Most children who develop diabetes early are more at risk of developing long-term complications. In addition, many countries in the African region are yet to prioritize diabetes in their health systems despite evidence of the health and economic effects of the disease[83]. Although, a lot of research has been done worldwide to determine and document the increasing incidence of T2D, comparatively very little attention has been focused on type 1 diabetes in the developing countries. Therefore, more efforts are needed in the African region, especially in sub-Saharan African countries to collect data and generate enough evidence in order for the governments of this region to see the impact of type 1 diabetes in this vulnerable group.

1.2.2. Within country variation.

Within-country variation in incidence rates has been reported in some of the Scandinavian and European countries such as Sweden[84], Finland[85], Italy[86] and Sardinia[87] with a 5-fold higher rate in the island of Sardinia compared to mainland Italy[75]. Also, a higher incidence in the rural than in the urban areas has been shown in studies from Finland[88], Sweden[89] and Northern Ireland[90]. On the contrary, reports from Lithuania[91] and Italy[86] have shown the opposite.

Geographical variability in incidence rates among children with T1D may be associated with ethnic differences and socioeconomic variables between rural and urban areas as well as population density.

1.2.3. Ethnicity.

According to the SEARCH for diabetes in youth study, T1D incidence rates vary remarkably between races and ethnic groups. Also, the risk is much higher among Caucasians, less in African – American blacks and extremely low in Asians and Pacific Islanders and this is strongly related with incidence variation across countries.

In addition, available data from the SEARCH study reported T1D incidence to be highest among non-Hispanic white children with a slightly higher incidence rate for males than females (24.5/100,000 for males and 22.7/100,000 for females) followed by African-American youth (15.7/100,000) for those 0 - 9 years old and 10 - 19 years old during 2002 – 2005) and for Hispanic youth (16.2/100,000 and 15.0/100,000) for boys and girls aged 0 - 14 years.

A migrant study among German residents, comparing the incidence of T1D in German children as opposed to Italian children originating from a very high-risk region (Sardinia) and from areas of medium-risk (continental Italy) indicated that children from Italy with T1D had incidence rates that were nearer to those of their country of origin than to those of German children[92]. This finding points to the fact that genetic factors play a powerful role in the development of T1D. Incidence rates were lowest among Asian and Pacific Islanders youth (6.4/100,000 and 7.4/100,000 in those 0 – 9 years and 10 – 19 years of age respectively)[75].

1.2.4. Seasonality at diabetes onset.

Many studies in the developed world have found evidence on a seasonal pattern in the onset or diagnosis of type 1 diabetes in children with a peak during the colder months as opposed to the warm months. However, the results so far are conflicting. Although some studies have found evidence for seasonality[93,94], a study by Padaiga *et al.*[95] did not while another study only found seasonality in subpopulation groups[96]. Also, seasonal variation at diagnosis appeared to be different in the younger and older children implying a possible role of environmental factors in the development of the disease.

1.2.5. Seasonality at birth.

With regards to seasonality at birth, several epidemiological studies have also reported a seasonal pattern at birth with a higher incidence for children born in summer and spring compared to those born in autumn and winter[94,97]. Notwithstanding, little evidence has been found to support the theory that environmental factors operating during foetal or neonatal life as a result of a particular season have any influence on type 1 diabetes development later in life[98].

1.2.6. Age

Type 1 diabetes incidence shows an age-dependent pattern with the incidence increasing from birth to 12 years, with a peak between 10-14 years of age, before dropping to a much lower rate[99]. Nevertheless, studies from African populations among type 1 diabetics have shown a peak incidence to occur a decade later (i.e. 20 – 29 years of age) compared to what is seen in Caucasians[100]. In addition, the reasons for this delayed age at diabetes onset among Africans are still unknown. A study in rural Ethiopia showed that the disease phenotype observed in this part of Africa was mostly among young adult males and it was different from the classical form of T1D observed in Western countries but conformed to the descriptions of malnutrition – related diabetes, a category of diabetes which is not recognized in the current classification of diabetes by WHO[100]. Also, the rising worldwide incidence of type 1 diabetes is especially marked in the youngest children (0 – 4 years)[101].

1.2.7. Gender

Although data from different regions suggest that in populations of high – incidence there is a slight male excess and a minor female excess in low-incidence populations[91], on average both genders carry similar risks. While male excess has been observed among populations of European origins, a slight female predominance has been reported in African populations. For instance, studies carried out in Egypt and South Africa among children with type 1 diabetes, reported a slightly higher incidence among females compared to males[102,103] with most of the cases coming from the rural areas. In contrast, a study which was carried out among children with type 1 diabetes in Nigeria reported a male predominance[104].

1.3. Diagnosis, presentation, management and complications of diabetes mellitus.

1.3.1. Diagnosis of type 1 diabetes.

Diabetes in children usually present with characteristic symptoms such as unexplained weight-loss, polyuria, ketonuria, polydipsia, blurring of vision, glycosuria as well as drowsiness and coma in severe cases[1,105] and clinical diagnosis of diabetes is often prompted by these symptoms. Current guidelines of the American Diabetes Association (ADA) recommend that diagnosis of diabetes in children and adolescents should be done using the World Health Organization (WHO) report of 1999[106] and the guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD)[105]. The diagnostic criteria for diabetes are based on the presence or absence of characteristic symptoms and additionally on any of the criteria below[107]:

Table 1.3: Criteria for diagnosing diabetes according to the American Diabetes Association (ADA)[107].

1	HbA1c † ≥ 6.5 %. This test should be done using an NGSP certified method and standardized to the DCCT† assay.*
	OR
2	FPG† ≥126mg/dL (7.0 mmol/L). Fasting is defined as no intake of food for at least 8 hours.*
	OR
3	Two-hour plasma glucose ≥ 200 mg/dL or 11.1 mmol/L during an OGTT†. This test should be performed according to World Health Organization criteria, using a 75 g of glucose dissolved in water.*
	OR
4	Patients with classic symptoms of high blood sugar or a random plasma glucose ≥ 200 mg/dL or 11.1 mmol/L.

*In the absence of unequivocal hyperglycemia, the test can be repeated to confirm the results. †HbA1c, glycosylated haemoglobin; NGSP, National Glycoheamoglobin Standardization Program; FPG, Fasting plasma glucose; OGTT, Oral glucose tolerance test; DCCT, Diabetes Control and Complications Trial.

The current guidelines published by the World Health Organization (WHO) done in consultation with the International Diabetes Federation (IDF) in 2006 recommends using

fasting plasma glucose values of ≥ 126mg/dL (7 mmol/l) or a 2 hour plasma glucose value of ≥ 200 mg/dL (11.1 mmol/l) during an OGTT as diagnostic criteria. In addition, diagnosis of diabetes should be standardized to the Diabetes Control and Complications Trial (DCCT) assay.

1.3.2. Clinical presentation of diabetes in children and adolescents.

Pediatric type 1 diabetes is characterized by stages ranging from an asymptomatic preclinical phase, clinical presentation, partial remission or honey moon phase and finally a chronic established lifelong insulin-dependent phase[108]. Preclinical diabetes is the phase before clinical presentation during which markers of autoimmunity may be identified.

Depending on the type of diabetes and age at onset, manifestation may differ from patient to patient given the fact that the time interval between abnormalities in glucose control until the development of symptoms is usually very brief. Children with type 1 diabetes usually present with classical symptoms such as polydipsia, polyuria, polyphagia and weight loss. In addition, most children with type 1 diabetes present with metabolic deterioration leading to diabetic ketoacidosis (an event which is life threatening), presenting with nausea, lethargy, vomiting and dehydration[109].

After clinical diagnosis and following initiation of insulin therapy is the honeymoon or partial remission period during which the insulin requirement in about 42% - 80% of children and adolescents decreases transiently while good glycaemic control is maintained[110,111]. This has been associated with the fact that the remaining beta cells that are exhausted but not yet destroyed restore endogenous insulin production with the alleviation of hyperglycemia[111,112]. The partial remission phase usually commences within days to weeks after the start of insulin therapy and may last for weeks to months[108]. A study has reported that the mean duration of the partial remission period is 11.7 +/- 8.9 months[113] and in some cases the requirements for insulin may decrease to the point of being able to temporary withdraw insulin therapy and still be able to maintain normoglycaemia[108,114]. This partial remission phase is always short-lived and evolves to the lifelong insulin dependence chronic phase. Therefore, in certain cases, the diagnosis of diabetes should be considered in the absence of the classic symptoms. For instance, in children who present with an acute

febrile illness from whom elevated plasma glucose levels are obtained as part of their laboratory diagnosis.

1.3.3. Management of type 1 diabetes in children and adolescents.

The management of diabetes involves continuous medical care and patient self-management education in order to prevent acute complications[107] such as diabetic ketoacidosis (DKA) and hypoglycemia which are the major causes of morbidity and death in younger patients[61,115] and the risk of long-term complications[116,117]. Therefore, prevention of long-term complications is the major focus of diabetes management in younger and adolescents patients with longer diabetes duration. However, pediatric diabetes management has remained a major challenge to the patient, the healthcare provider as well as family members of the patients[118,119,120].

Current recommendations emphasize on the use of intensive insulin therapy which can either be administered by the use of multiple insulin injections (3 – 4 injections a day of basal and prandial insulin) or a continuous subcutaneous insulin infusion (CSII)[121]. Blood glucose monitoring as well as dietary and lifestyle modification have also been found to play an important role in the management of the disease[122]. Despite, the recommendations for the proper management of type 1 diabetes in children and adolescents, the anticipated improvement in glycaemic control is still to be achieved in all settings.

Glycaemic control.

The Diabetes Control and Complication Trial (DCCT), in individuals with T1D, demonstrated that strict glycaemic control delayed the onset as well as slowed the progression of long-term complications such as kidney disease, nerve problems and visual problems by 35-76 %[116,123]. Glycaemic control is routinely monitored by the use of glycosylated haemoglobin (HbA1c). Its value indicates the glycaemic control over the past 2 to 3 months; values below 7.5% are considered better according to the American Diabetes Association (ADA) standards for diabetes care[107]. Also, it is the most reliable method used to set the target values for glucose control and for evaluating treatment effectiveness[117].

The current guidelines of the ADA recommend an HbA1c goal of < 7.5% across all pediatric age-groups[107]. However, individualization is still encouraged. For instance, an HbA1c of 7.5% - 8.5% , < 8% and < 7.5% for children less than 6 years, 6 – 12 years and 13 – 19 years respectively[122]. These recommendations considered the benefits of strict glycaemic control against the risk of hypoglycemia especially in the younger patients[107,124], given the detrimental effects of hypoglycemia to the developing brain of younger patients. The adolescence group had a 0.5% higher HbA1c target than the recommendation for adults with T1D because this is a period of hormonal changes and achieving target HbA1c levels might be very challenging. Furthermore, although the current recommendations from the ADA[107] state that good glycaemic control is HbA1c < 7.5%, these goals are very difficult to achieve even in clinical trial settings. Even so, for individuals with severe anaemias especially in sub-Saharan Africa, HbA1c might not be a very good marker for glucose control since it gives falsely low readings, thus potentially reducing its usefulness in this region of the world.

There exists a wide variation in the level of glycaemic control in children with T1D between Africa and the developed economies. Glycaemic control in children with type 1 diabetes is improving in the industrialized countries while that is not the case in the African region[125,126]. For instance, in the American-based SEARCH for diabetes in youth study, a mean HbA1c of 8.18% was reported[73], while in the largest study from German and Austrian pediatric T1D (27,035 children with T1D in 207 pediatric centers) showed a median HbA1c value of 7.8%[127]. Comparatively, studies in Sudan[128] and Tanzania[126] have reported mean HbA1c of 9.3% and 10.65% respectively.

Blood glucose monitoring.

Self-monitoring of blood glucose is one of the key components in the management of type 1 diabetes in children and adolescents since it plays a vital role in evaluating individual response to therapy[107]. Also, this helps in preventing acute and chronic complications[122,129], thereby preventing many hospitalizations[130]. Based on these blood glucose results the physician can be able to alter the insulin regimen for the patient accordingly.

Current guidelines of the ADA recommend that patients with type 1 diabetes measure their blood glucose at least 6 to 8 times a day[107,117]. However, recommendations for the number of checks per day vary for each individual, depending on different factors (e.g. insulin regimen, diet and the ability to responsibly manage T1D) as well as the clinical needs of the patient. For instance, it is recommended that type 1 diabetics should check their blood glucose at least 4 times a day[131]. In addition, patients in the intensive treatment group of the Diabetes Control and Complications Trial[116] performed at least 4 blood sugar measurements every day. Therefore, for all people with diabetes, 3 or 4 blood sugar checks a day is a reasonable goal. Several studies have shown that there is a strong correlation between the glycaemic control and the frequency of blood glucose monitoring daily among children with type 1 diabetes[119, 132].

For example, a study by Ziegler *et al.*[133] involving 26,723 type 1 diabetic children and adolescents aged 0 – 18 years found that increased frequency of self-monitoring of blood glucose daily was related to better metabolic control in adolescents above 12 years of age but not in younger children irrespective of the treatment regimen. Similarly, a Danish nationwide study among type 1 diabetes patients aged 0 – 14 years diagnosed from 1996 to 2006 reported a reduction in HbA1c with increased frequency of self-monitoring of blood glucose[125]. Also, Murata *et al.*[134] in a study among adult patients with type 1 diabetes in Japan found that individuals who measured their blood glucose at least 3.5 times a day had improved glycaemic control compared to patients who did less than 3.5 measurements daily. Notwithstanding, the relatively small sample size and cross-sectional nature of the study are limiting factors in the ability to establish a causal relationship between blood glucose monitoring and HbA1c. On the contrary, self-monitoring of blood glucose was not found to be associated with better glycaemic control among Sudanese patients with diabetes[135]. Nevertheless, this study involved men and women with type 1 and type 2 diabetes and the results may not be reflective of the situation among children and adolescents with type 1 diabetes.

Diet and physical activity.

Diet as well as physical activity plays a vital role in the management plan of type 1 diabetic subjects. However, it is the most difficult aspect of treatment in children and adults. Current recommendations for diet in children and adolescents with type 1 diabetes are focused on achieving normal blood glucose levels without being accompanied by excess hypoglycaemic episodes[124], meanwhile for physical activity, they are advised to perform moderate physical activity for at least 60 minutes/day[107]. Proper nutrition is essential for growth and energy with close adherence to dietary recommendations playing a significant role in improving glucose control in children and adolescents[136].

Studies have demonstrated the influence of physical activity on glycaemic control in children with type 1 diabetes. For instance, a study by Cuenca-García *et al.*[137] among children 8 to 16 years from a Paediatric Diabetes Service in South West England showed that moderate-to-vigorous physical activity was associated with improved glycaemic control. Similarly, a meta-analysis by Miculis *et al.*[138] has also shown that physical activity plays a vital role in the treatment of children and adolescents with type 1 diabetes.

1.3.4. Complications of diabetes mellitus.

The biochemical alterations in type 1 diabetes results in complications which can be divided into short-term or acute complications (hypoglycemia and diabetic ketoacidosis) and long-term or chronic complications (i.e. microvascular and macrovascular). The components of microvascular complications include nephropathy, retinopathy and neuropathy (outcomes are visual impairment and blindness, renal failure, hypertension as well as muscle weakness and autonomic dysfunction respectively), while the components of macrovascular complications include, cardiovascular, cerebrovascular and peripheral vascular diseases[139]. A majority of the chronic complications are being attributed to the non-enzymatic glycosylation of protein residues in the nerves, blood vessels and renal glomeruli[140,141].

In developed countries, enormous efforts have been made to reduce chronic complications of diabetes; meanwhile the same cannot be said about developing countries especially sub-Saharan Africa. Also, the management of complications in many developing countries is very difficult due to paucity of data on the true burden of the disease among diabetic

children; although high rates of microvascular and macrovascular complications of the disease have been reported among adults. Nevertheless, the occurrence of new cases of paediatric T1D in many sub-Saharan countries has been reported alongside the growing disease prevalence, demonstrating the importance of assessing for chronic complications[142, 143].

Diabetic ketoacidosis (DKA).

Diabetic ketoacidosis is an acute life threatening metabolic deterioration which is characterized by ketonuria, high blood sugar and acidosis. It presents in 15% - 70% of children and adolescents newly diagnosed of type 1 diabetes [141] and it is a major cause of morbidity and mortality[61,144]. Children who present with diabetic ketoacidosis usually manifest as dehydration, vomiting, abdominal pain, acidotic breathing or rapid deep respiration (or Kussmaul's breathing), altered mental status and coma[109]. There seem to be a wide variation in the range of children presenting with diabetic ketoacidosis at diagnosis depending on the study population. A study has reported DKA at diagnosis to be more common among children in developing countries partly because access to medical care is limited and practitioners are less familiar with the symptoms of DKA[145].

Previous studies have reported the frequency of DKA to vary from 80% to 88%[80,146,147]. For instance, in Tanzania, 75% of children presented with DKA at diagnosis[125], while in Saudi Arabia, 79.8% of children with newly diagnosed type 1 diabetes presented with DKA[148]. Also, a study in Iran reported that 24% of children presented with DKA at diagnosis[149]. Nonetheless, DKA still remains a significant complication of type 1 diabetes which is associated with a variety of adverse events[150]. Therefore, focus on early diagnosis and intervention in children who have been newly diagnosed with the disease might help in reducing the frequency of DKA.

Hypoglycemia.

Hypoglycemia is the most frequent acute complication of type 1 diabetes and it is a limiting factor in attaining glycaemic targets in paediatric diabetic patients[151,152]. Although, it may become life-threatening, it rarely leads to death if left untreated since hypoglycaemia

activates a counter regulatory system of stress hormones in order to stop the glucose level from dropping thereby bringing about unpleasant symptoms, such as rapid heartbeat, increased sweating, shaking, hunger and difficulty in concentrating.

Studies have shown that hypoglycemia appears to be more common among premature newborns[153, 154] and it has been reported that more than 80% of admissions from the nursery to the neonatal intensive care unit in Japan are due to hypoglycemia or apnea[155]. However, it has been reported that hypoglycaemic episodes decrease with age[156]. The few studies carried out in Africa have reported a high prevalence of severe hypoglycemia (25% - 55%)[157,158] which can be attributed to a lack of awareness among family members and healthcare workers and in most cases lack of blood glucose monitoring at an individual or hospital level.

Diabetic Nephropathy.

Diabetic nephropathy is persistent proteinuria in people who do not have urinary tract infection or any other disease that can be causing the proteinuria. Elevated plasma glucose levels play a significant role in the development of diabetic nephropathy[159], given the fact that it positively regulates the expression of a transforming growth factor-β which is involved in the early stages of the disease. Despite, a decline in the incidence of complications being reported in many areas with specialized diabetes clinics[160,161], diabetic nephropathy remains a major cause of morbidity and mortality among youths with T1D[161]. The cumulative prevalence of microalbuminuria (a marker of future renal failure) in childhood onset of T1D is between 25.7% – 50.7% after 10 – 19 years of diabetes[162], with rates varying between 50% – 80% across different studies[142, 162,163 164]. However, studies by Finne *et al.*[166] have shown a decline in the rate of progression to advanced nephropathy.

Among children with type 1 diabetes in sub-Saharan Africa, very little is known with regards to the epidemiology of chronic kidney disease (CKD). Nevertheless, the available data in the region is mostly on adults indicating an overall prevalence of 13.9%[167]. In addition, there seem to be no significant difference in chronic kidney disease prevalence between the urban (12.4%) and rural (16.5%) settings. However, microalbuminuria which is a marker of nephropathy among adult type 2 diabetic patients in Cameroon was found to be

53.1%[168], whereas, the prevalence of microalbuminuria in type 1 diabetic children was estimated at 29.3% in Tanzania[126].

Diabetic nephropathy remains a complication associated with generalized microvascular[169] and macrovascular[170] damage, and in those with type 1 diabetes onset under the age of 20 years, it increases mortality[171]. Therefore, it is important to carefully monitor all children with T1D to ensure diabetes control is optimized and to look for evidence of early renal disease, given the fact that persistent microalbuminuria is predictive of later development of renal failure in T1D patients[172].

Diabetic retinopathy and neuropathy.

Diabetic retinopathy is the most common cause of acquired blindness in the world, with a prevalence rate of about 20% – 25% in type 1 diabetics[173]. Retinopathy and neuropathy are unlikely to develop before the age of 15 and in patients with less than 5 years of diabetes duration[174]. An epidemiological study has shown that there exist a close relationship between diabetic nephropathy and retinopathy[175]. Although, diabetic neuropathy is rarely reported in children, screening is recommended for the other microvascular complications.

In Cameroon, diabetic retinopathy in adults with type 2 diabetes was estimated to be 40.3%[176]. However, this study finding cannot be generalized for all the patients with type 2 diabetes in the country because, the study was carried out in an urban setting excluding diabetic patients living in the rural areas and those of low socioeconomic status. Also, Majaliwa *et al.*[126] reported a prevalence of diabetic retinopathy of 22.68% among children and adolescents in Tanzania with a higher frequency being found in the age group before puberty.

Macrovascular complications.

Children with type 1 diabetes have a 10-fold higher risk of developing cardiovascular disease compared to individuals without diabetes[174]. Cardiovascular disease risk factors in childhood include the presence of obesity, smoking, microvascular complications, dyslipidemia, hypertension and a family history of premature cardiovascular disease[177, 178]. In addition, the presence of cardiovascular risk factors in children has also been shown to be

associated with accelerated atherosclerosis[179,180]. The increasing prevalence of obesity globally has also affected children with T1D and has led to a rise in the associated risk factors for macrovascular disease[181, 182]. Previous research in a Dutch cohort of 283 children age 3-18 years with a mean duration of diabetes of 5.3 years, reported that 38.5% of the children were overweight or obese, 13.1% hypertensive and 17.3% found to have elevated LDL cholesterol[183]. Similarly, one or two cardiovascular risk factors have been reported among children with type 1 diabetes in other studies[184, 185].

Epidemiological data on chronic complications of diabetes in the African region is limited[186] with cardiovascular disease complications related to diabetes also thought to be rare but they are currently on the rise[187]. A study by Tamba *et al.*[188] in 2013 among adult diabetics in Cameroon reported the prevalence of coronary heart disease to be 23.6%. However, the authors indicated that the results might have been influenced given the retrospective nature of the study and lack of recommended tools for the proper diagnosis of diabetes complications. Therefore, in children and young adults with T1D, early detection and proper management of cardiovascular risk factors is very important. For example, the Epidemiology of Diabetes Interventions and Complications study (EDIC), a follow up study of the DCCT, showed that intensive insulin treatment decreased long-term macrovascular complications in T1D patients[189].

1.4. Predictors/determinants of treatment outcome as measured by glycaemic control.

Given the benefits of strict glycaemic control, a study had described potential factors (demographic and diabetes-related characteristics) in children and adolescents with type 1 diabetes associated with better glycaemic control[190] and these factors differ between children and adults. However, these factors have been identified in developed countries and it is unclear whether the same or other factors determine glucose control in settings with very limited health resources. This is especially important because there is improved glycaemic control in children with type 1 diabetes in industrialized countries while it seems not to be improving in sub-Saharan Africa[125,126,127,128]. Some of the factors predictive of a patient's glycosylated haemoglobin (HbA1c) level are discussed in the following paragraphs:

1.4.1. Age and diabetes duration.

The age of the patient, age at onset and duration of diabetes have been shown to be significantly associated with the level of glycosylated haemoglobin of children with type 1 diabetes[119,191,192]. Studies in the UK and France[193] have shown that older age and longer duration of diabetes are associated with poor glycaemic control. A study among type 1 diabetics in Wales[194] to identify factors associated with glycaemic control reported that glycaemic control was worse among older children compared to the younger ones. Similarly, a study involving 2,218 pediatric patients with type 1 diabetes in the USA indicated that older age at onset was a risk factor for poor glycaemic control[192]. On the contrary, age was not associated with poor glycaemic control in studies from Australia and New Zealand[195,196].

Studies have also demonstrated that glycaemic control gets worse with increasing duration of diabetes[192,197]. However, a study in Sudan showed an inverse relationship[128].

1.4.2. Socioeconomic status (SES).

Socioeconomic status (SES) usually defined as occupation, educational level, and household income has become an important determinant of glucose control among type 1 diabetics [189,198,199]. Recent studies have associated socioeconomic variables such as family income, level of maternal education and family structure[119,195,200] with glycaemic control among children with type 1 diabetes. Also, McKinney and colleagues[193] observed that patients from deprived areas had poorer glycaemic control compared to those from affluent areas. In addition, studies in the USA and France have reported better glycaemic control among children from high socioeconomic backgrounds[197, 201]. However, that was not the case in Egypt[202].

Moreover, a study from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) among youths with type 1 diabetes found glycaemic control to be significantly associated with SES[203].

1.4.3. Family living arrangements.

Family living arrangements has also been found to be an important predictor of glucose control in children and adolescents with type 1 diabetes. Some studies have shown better glucose control among children/adolescents who live with both biological parents compared to children who came from single parent families[200,204].

Similarly, Thompson *et al.*[205] found a 1.2% higher HbA1c in children from single mother families compared to those from two parent families. The authors attributed this to the lower income status and educational level of single mothers.

1.4.4. Family involvement in diabetes-related tasks.

The family environment where parents and guardians are actively involved in caring for children and adolescents with type 1 diabetes has been found to be associated with improved glycaemic control among patients[206]. In addition, family support and involvement of parents/guardians in the diabetes-related tasks of their children has been found to promote adherence and a better glycaemic control.

For instance, a study by Anderson *et al.*[207] found that more parental involvement in blood glucose monitoring (BGM) improved adherence and this translated to a better outcome. Also, Pereira *et al.*[208] in Portugal found that support for female diabetics and those of the lower social class resulted in higher adherence and better metabolic control while family conflict in patients of the upper social class predicted poor glycaemic control. In addition, a recent meta-analysis by Tsiouli *et al.*[209] demonstrated that family involvement in the treatment of young patients with type 1 diabetes resulted in improved glycaemic control, while family conflict was negatively correlated with the glycaemic control of the patient.

1.4.5. Gender.

Glycaemic control has been shown to differ across gender with females more likely to be poorly controlled than males[191,202]. In a multicentre study from Austria and Germany (involving 27,035 participants), girls on average had a higher mean HbA1c than boys[127]. Also, in a study by Cutfield *et al.*[200] in the Auckland region a significant association between gender and glycaemic control was reported with females exhibiting worse glycaemic control

compared to males. Similarly, gender was significantly associated with glycaemic control in a study from Egypt[202]. This Egyptian study indicated a high percentage of poor glucose control among girls older than 15 years compared to boys of the same age group.

1.4.6. Regularity of clinic visits.

The number of clinic attendance has been found to be predictive of a patient's glycaemic control with fewer clinic visits being significantly associated with poorer control in children/adolescents followed up at diabetes centers[210,211,212]. However, studies in Tanzania and Portland [126,212] did not find any association between increased frequency of clinic attendance and glycaemic control.

1.4.7. Insulin dose.

The dose of insulin has also been found to be associated with the level of glycosylated haemoglobin. A higher dose of insulin per kg body weight has been found to be associated with poor glycaemic control in studies from France, New Zealand and Australia[195,196,198]. However, a study in Sudan demonstrated no difference in glycaemic control with a higher dose of insulin[128].

1.4.8. Adherence to treatment regimens.

Adherence to the different treatment regimens represents an important factor in determining good glycaemic control and eventually a better treatment outcome. A recent meta-analysis by Hood *et al.*[121] demonstrated a negative correlation between adherence and HbA1c levels in children and adolescents with type 1 diabetes and this was observed to be independent of sociodemographic and other diabetes specific variables. Mehta *et al.*[213] demonstrated that greater adherence to diet was associated with lower HbA1c levels in youth with diabetes. Nevertheless, the cross-sectional design of the study limits the ability to establish causal relationships between dietary adherence and HbA1c.

In addition, blood glucose monitoring adherence has also been found to be predictive of glycaemic control among children with type 1 diabetes with less frequent blood glucose monitoring resulting in poor glycaemic control[134,192,193]. Further, a study in Denmark

showed that glycaemic control improved with more frequent self-monitoring of blood glucose[123]. Similar results were reported in a study involving 26,723 children and adolescents aged 0-18 years with type 1 diabetes from 233 centers in Germany and Austria[132]. This finding was also confirmed in Sudan[135].

1.4.9. Primary caregiver.

The primary caregiver involved in the care of children with type 1 diabetes is an important predictor of the glycosylated haemoglobin level of the patient. Several studies[214,215,216] have indicated that the mother is most often the primary caregiver involved in the care of the diabetic child. Parental education and the active involvement of parents in the child's diabetes self-management are crucial elements in achieving good glucose control. Al-Odayani *et al.*[214] found that type 1 diabetic children of mothers with higher level of education and more knowledge of diabetes irrespective of SES were better controlled resulting in a decrease in acute and chronic complications of diabetes in these children.

1.4.10. Caregiver diabetes knowledge and literacy.

Diabetes knowledge of the family/caregiver plays an important role in improving the glycaemic control of children with type 1 diabetes. Evidence has shown that parents/caregivers/mothers with more knowledge of diabetes and better education results in lower HbA1c levels of their children[214,216,217,218]. Also, the attitude of parents and caregivers towards the care of children with diabetes has been found to be predictive of glycosylated haemoglobin levels[196]. For example, a study by Butler *et al.*[119] to identify modifiable family factors that influence glycaemic control in youth with type 1 diabetes beyond the environment found that higher parental diabetes-specific knowledge and less parental-perceived burden towards the care of diabetic children were predictive of HbA1c levels. In addition, Soheilipour *et al.*[219] found that disease awareness of mothers of type 1 diabetic children results in improved blood sugar control. Moreover, a study by Hassan and Heptulla[220] found that literacy and numerical skills of caregivers influences significantly the glycaemic control of children with type 1 diabetes. Nonetheless, the voluntary nature of the

study might have excluded the less educated who often are unlikely to access outpatient care and have a sense of shame as a result of their illiteracy.

In contrast to the above, an Indian study by Vimalavathini and colleagues[221] observed that planned educational intervention programs on the attitudes, knowledge, and practices of type 1 diabetics resulted in a significant improvement in the knowledge and attitude but no improvement in HbA1c levels. Therefore, assessing literacy/numeracy skills of caregivers and addressing any deficiencies may be crucial in optimizing glycaemic control among children with type 1 diabetes.

1.5. Challenges in diabetes management.

Effective diabetes management requires a complex and demanding balancing of insulin dosing, exercise and diet alongside with frequent blood glucose monitoring which can be very challenging even to the most motivated patient. In the industrialized nations, enormous efforts have been made to manage type 1 diabetes and reduce chronic complications of the disease, while in many developing countries, there is limited clinical and metabolic data on the disease in children making its management even more difficult[126]. Despite advances in insulin therapeutics, adherence to diabetes regimens is often very difficult for patients of all ages especially adolescents[122,222]. This is due to the fact that they undergo physiological changes during adolescence years causing greater insulin resistance and making it difficult for them to achieve and maintain the target glycaemic level[116].

Given the poor health seeking behaviour in developing countries and lack of quality health care, most children present late resulting in a majority of children dying early due to complications[223]. Also, some of the major challenges to type 1 diabetes management in sub-Saharan Africa include; missed and delayed diagnosis as well as insulin unavailability[224] as opposed to developed countries. For instance, a Sudanese study reported that about 10% of children were not admitted at the time of diagnosis but were only admitted after they had developed DKA[81]. Another difficulty among children with type 1 diabetes in sub-Saharan Africa and other low income countries is that most of the children with diabetes are treated by an adult diabetic endocrinologist. This results in marked deficiencies in providing

information to children with diabetes and members of their families on the management of the disease.

In addition, the cost of management of the disease is very high in developing countries where a majority of the population is living below the poverty line. Also, traditional healers are an integral part of most healthcare systems in some African and other less developed countries[225] and some patients often visit the local traditional healers before coming to the hospital[226]. Traditional medicine or alternative medicine refers to health practices or approaches, beliefs and knowledge of incorporating animal, plant as well as mineral based medicines and spiritual therapies in combination to diagnose, treat, and prevent illnesses[223].

1.6. The situation in Cameroon.

In Cameroon, there is a low prevalence of type 1 diabetes among children, partly due to the fact that most of the cases are not diagnosed and only a few of the children diagnosed live long enough after diagnosis given the poor prognosis associated with the disease. As of 2014, there was no data on the number of children living with type 1 diabetes in Cameroon[14]. The most reliable information comes from the program "Changing Diabetes in Children" (CDiC), a partnership initiative with Novo Nordisk and the local governments of some low-and-middle income countries which aims at improving on the capacity of the healthcare personnel and the healthcare system for the proper management and early diagnosis of T1D in children[64]. The CDiC program has been set up in 8 out of the 10 administrative regions of the country and a diabetic register for prospective follow-up of patients aged 0 to 18 years has been established since 2010. As of November 2014, figures from the Cameroon Diabetic Association indicated that a total of 336 children with type 1 diabetes are enrolled in the CDiC program. So far, 6 children have died, one from the Littoral and 5 from the North West Region. Therefore, the identification of factors associated with the outcome of patients in our setting is essential in order to establish appropriate interventions to prevent chronic complications and those at risk of acute complications.

Also, Cameroon still has a limited number of pediatric endocrinologists that can give informed advice on the management of the disease to these children and their parents/caregivers. There is therefore a need for the medical schools in the country to start offering specialist programmes in pediatrics to help prospective health professionals to acquire the necessary skills required for early diagnosis and adequate management of type 1 diabetes among children in the country.

1.7. Statement of the problem.

Like the rest of the world, most countries in sub-Saharan Africa (SSA) are also having children suffering from type 1 diabetes which is associated with a high mortality rate and mostly the poor are being affected by the disease[64,67]. In contrast to Western countries, type 1 diabetes is associated with a very poor prognosis in sub-Saharan Africa with many patients not being diagnosed and those diagnosed having a dramatically reduced life expectancy (usually less than one year)[64,82]. In addition, this disorder was thought to be rare in rural Africa[65]. Moreover, there are many barriers to appropriate diabetes care for children living with diabetes in the region such as inadequate healthcare systems, lack of trained health personnel and inability of the patient or family to afford treatment (i.e. insulin, syringes and blood glucose monitoring equipment). Despite the fact that type 1 diabetes is a treatable disease, it is associated with a poor prognosis in Cameroon.

In Cameroon, information on factors associated to the outcome of children living with type 1 diabetes is limited. If efforts are not made to understand the contributing factors to good or poor glucose control, the number of children affected will keep increasing and this will lead to an increase in the number of families affected posing an emotional and financial burden on them. Also, it will affect the sustainability of the fragile healthcare system which is already overburdened with communicable diseases. In Cameroon, the CDiC program has helped in increasing access to care for children suffering from type 1 diabetes[64] thereby improving on the health status and the quality of life of these children. According to the International Diabetes Federation[14], over half a million children below the age of 14 are estimated to be living with type 1 diabetes with an estimated 46,400 of these children in the African region[14]. Despite the above evidence, there is no information on the prognosis of the

disease in Cameroon children. In developed countries, a variety of factors that predict glucose control in children with type 1 diabetes has been documented[125,187,192] and it is unclear whether the same or other factors determine glucose control in settings with very limited health resources like Cameroon.

This study was done to identify the factors (predictors) of good and poor glucose control in children and adolescents with type 1 diabetes included in the Cameroon childhood diabetes registry. The findings from this study will help to define strategies which will ultimately help to improve the prognosis of these children in Cameroon (and probably other countries of sub-Saharan Africa). Also, it will create valuable data for the healthcare system of Cameroon and guide targeted interventions. In addition, it will help the responsible persons of the registry to adjust their approaches and thus hopefully result in good outcome for more children.

1.8. Objectives of the study.

Type 1 diabetes mostly affects children[67] and its management remains a challenge to many sub-Saharan African families having a child with type 1 diabetes. Despite the fact that type 1 diabetes is a treatable disease, it is still associated with a poor prognosis in Cameroon. Factors that predict the outcome of children with type 1 diabetes have been identified from studies in developed economies and it remains uncertain whether these predictors contribute to the same extent in predicting glucose control in a setting with inadequate health resources like Cameroon. This is particularly important as there seem to be improved glycaemic control in children with type 1 diabetes in the developed countries[125,127], while it is not improving in sub-Saharan Africa[126,128].

This study therefore set out to identify the factors that predict good glucose control in children and adolescents with type 1 diabetes in the North West Region of Cameroon.

Specifically, this study:

- Determined the mean glycaemic control of the study population by age of patient and duration of diabetes.

- Examined the relationship between socio-demographic factors and diabetes-related factors on glucose control of children and adolescents with type 1 diabetes.
- Investigated the clinical and biochemical characteristics at onset of type 1 diabetes, the study period as well as gender and age group specific differences in clinical and biochemical characteristics.
- Investigated the impact of type 1 diabetes on the daily life of children and adolescents and its impact on glycaemic control.
- Determined the frequency of diabetic ketoacidosis at type 1 diabetes onset and the potential factors associated with DKA in newly diagnosed children with type 1 diabetes.

This study was designed to collect and statistically analyze information (predictors) to find out whether variables can be identified which predict why the course of the disease is better in some cases than in others. The measures of interest include sociodemographic characteristics, diabetes knowledge of the children, practices of patient/caregiver related to diabetes, insulin availability, the impact of type 1 diabetes on daily life as well as clinical/biochemical parameters.

2. METHODS

2.1. Study design/ population.

This study was a hospital based cross-sectional study, of data collected between January and August 2014, involving all the children and adolescents aged 0 to 18 years attending the clinics for children and adolescents living with diabetes in the North West Region of Cameroon. These clinics are specifically designed for the monitoring and appropriate treatment of these children. In addition, these clinics aim at educating the patients and their families on how to achieve the best possible glucose control.

The prospective registration of laboratory and clinical data at diagnosis as part of the Cameroon childhood diabetes register had started since 2010. Type 1 diabetes was defined according to WHO criteria based on a clinical diagnosis[106] by a physician with the date of onset being the date of diagnosis. A total of 76 children (35 boys and 41 girls) were involved in the study. Also, more than 60% of the study participants were from a rural setting and of low SES.

2.2. Study area and the management of patients.

This study was carried out in the children's diabetic outpatient clinics in the North West Region of Cameroon including; the Bamenda Regional Hospital and the Banso Baptist Hospital - Kumbo.

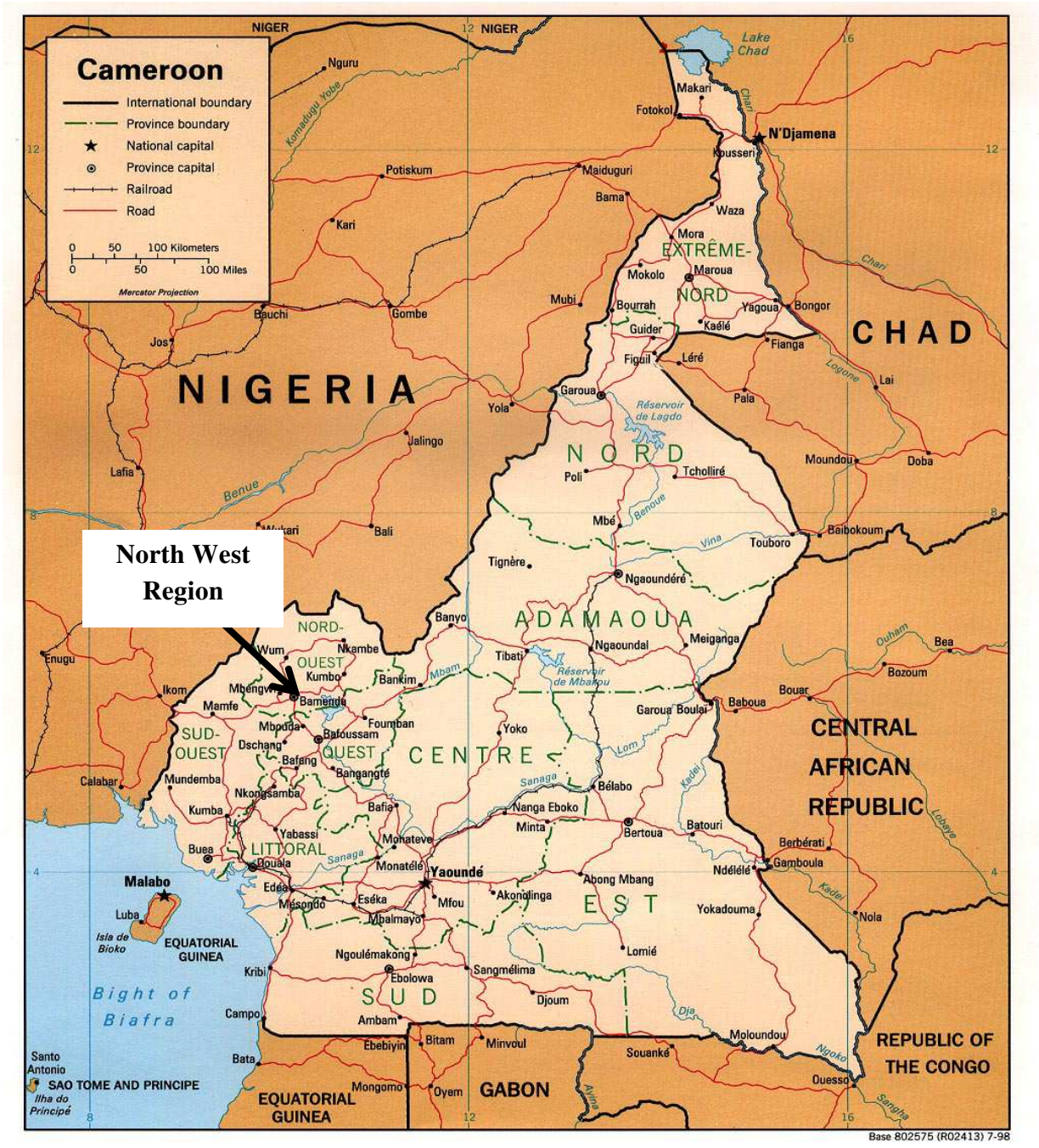

Figure 2.1: Map of Cameroon indicating the study area (North West Region).
Source: http://commons.wikimedia.org/wiki/Atlas_of_Cameroon

The North West Region is the third most populated region in Cameroon with Bamenda being the capital. The region is one of the two English speaking regions of Cameroon and Bamenda is one of the major towns including other smaller towns like Kumbo. Also, as of

2010, this region had an estimated population of 1.8 million[227] with a population density of 104.3 people /km^2. In addition, this region is also known for its academic activities including both English and French-speaking Cameroonians and currently has four universities (1 state university and 3 private universities). Cameroon like the rest of sub-Saharan African countries has been experiencing the epidemiological transition, and in 2002, Pasquet and colleagues[228] indicated that Cameroon has the highest urbanization rate in sub-Saharan Africa. It has been predicted that the rate of urbanization will reach 67% by 2025. The North West Region is no exception to this rapid urbanization process.

The pattern of food consumption follows three meals a day including breakfast, lunch and supper. In rural settings, the same food can be consumed during the three meals of the day with most of the staple food consumed during meals generally comprising of a starch component with either vegetables or soup with meat or fish depending on the SES of the family. In both the rural and urban areas of this region, occupations range from farming activities to businesses activities, white-collar jobs as well as students.

The main public hospital for the region is the Bamenda Regional Hospital and other private and faith-based hospitals such as the Banso Baptist Hospital, the Mbingo Baptist Hospital and the St. Elizabeth Catholic General Hospital, Shisong which increase access to healthcare in the region. The Bamenda Regional Hospital is located in the city's capital Bamenda and it remains the main epicentre for health in the region. Also, it serves as a referral hospital and provides health services to the more than 550,000 inhabitants of the Bamenda town and the entire population of the North West Region. The administration of the hospital is led by a director who in turn has several subordinates. Information from the Regional Delegation for Public Health for the North West Region indicates that the hospital has about 400 beds with about 350 trained health personnel and close to 49 ward assistants. Also, the hospital has over 21 departments located in one area of the hospital and 10 wards occupying another area. Access to the different hospital buildings is easy since the buildings are interconnected. Moreover, most of the buildings in the hospital are German style given the fact that Cameroon was initially a German colony. In addition, the Banso Baptist Hospital is the

oldest and one of the largest hospitals of the Cameroon Baptist Convention Health Board and it provides services to more than 100,000 patients annually. It is a 238 bed facility and the staff includes 5 physicians, an ophthalmologist, 2 surgeons, a Palliative Care physician and a dentist.

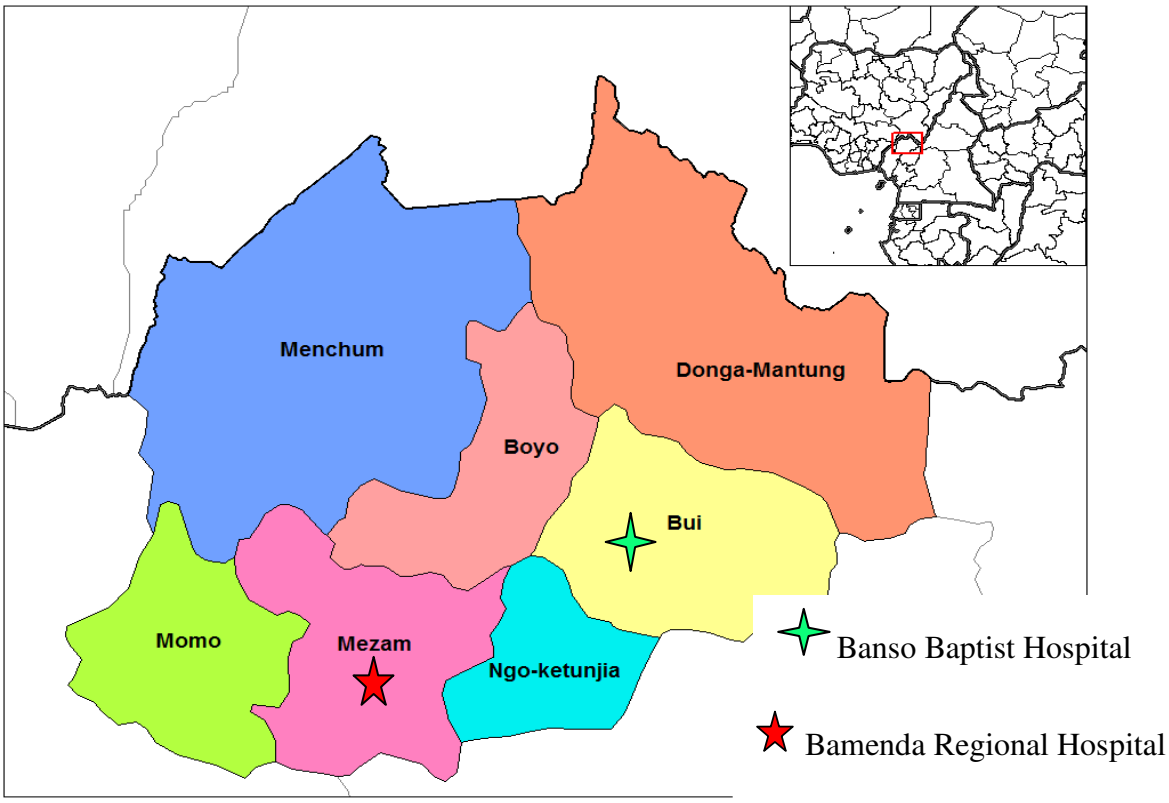

Figure 2.2: Map of the North West Region indicating the 7 divisions and the study sites (adapted and modified from http://en.wikipedia.org/wiki/Northwest_Region_(Cameroon).

The patients in these clinics are managed by a team of 2 diabetic nurses, 1 pediatrician and 2 support staffs. As of November 2014, the number of children and adolescents up to 18 years with type 1 diabetes registered in these clinics was 80. These clinics run once every week. At diagnosis data on, height, weight, baseline lipid profiles, HbA1c, urine dipstick, blood glucose and ophthalmologic examinations are done for all the patients. These children are reviewed at least once every three months by the diabetic nurse in charge of the clinic who also communicates with the physician in charge of the children regarding clinical care

issues. The diabetic nurse also follows-up on children who have missed their appointments by phone calls and identifies individual needs of the patients. HbA1c levels are monitored quarterly, while lipid profiles, serum creatinine, ophthalmologic examinations and thyroid function tests are repeated yearly. During subsequent clinic visits, height, weight, systolic and diastolic blood pressure, foot examinations and glucometer readings are reviewed.

On the first day to the clinic, patients and guardians are given diabetes education and advice on appropriate nutrition. The components of the nutrition guidelines include;

- Meal frequency which included 3 main meals and 3 snacks per day.
- Meal content which should include carbohydrates, proteins and vitamins which may be consumed with a reduction in the amount of carbohydrate to two thirds of the usual amount but an increase in vegetable consumption. In addition, fruits may be consumed but only a portion.
- Forbidden foods which included soft drinks, added sugar and animal fat.

In addition, all patients attending these clinics are provided with insulin at no cost through the International Diabetes Federation (IDF), "Changing Diabetes in Children" (CDiC) program. Also, they are provided with blood glucose monitors, glucose strips, and diaries for measuring and recording of their blood glucose at home. These children/adolescents are encouraged to monitor their glucose level at least 3 or 4 times a day and record the information in their diaries. The blood glucose levels are then used by the clinicians to alter appropriately the insulin regimen. The patients are either on a 2 daily insulin injection regimen or on a multiple insulin injection regimen.

A written consent that explained the purpose of the study was distributed to parents/guardians of the study participants and the heads of the clinics. Also, the research staff had to explain the purpose of the study to the participants before data collection. Those who consented to the study were asked to sign the consent form and assent was obtained from children above 10 years of age.

Inclusion criteria:

This study included children and adolescents up to 18 years inclusive, with type 1 diabetes and attending the clinics for children living with diabetes in the North West Region of Cameroon. Also, informed consent was obtained from parents/guardians or assent from adolescents.

2.3. Sample and sample size estimation.

The sampling technique used in this study was convenient sampling since the children involved are in an intervention program currently going on in the country.

The main aim of this study was to identify factors which predict good glucose control among children with type 1 diabetes using binary logistic regression as the main method of analysis. The sample size for this study was estimated using Hsieh's sample size formula/tables, which make use of binary logistic regression models with dichotomous covariates and a dichotomous dependent variable[229]. The main outcome variable (Y) in this study is HbA1c, which is an indicator of glucose control and it was assigned values of 0 for good glycaemic control and 1 for poor glycaemic control. An important covariate (X) in our study that is dichotomous is BGM adherence which was also assigned values of 0 and 1 for good BGM adherence and poor BGM adherence respectively.

The Hsieh's sample size formula used is below:

$$n < \frac{4P\,(1-P)\,(Z_{1-\alpha/2} + Z_{1-\beta})^2}{(P_1 - P_2)^2}$$

Where P is probability of Y = 1, i.e. probability of having poor glycaemic control, which was equal to 0.5, α is significance level (0.05), 1 – β is power (80%), $(Z_{1-\alpha/2} + Z_{1-\beta})^2$ is 7.84, P_1 is the proportion of subjects with poor glucose control among those with good adherence to BGM (i.e. proportion at X = 0), P_2 is the proportion of subjects with poor glucose control among those with poor adherence to BGM (i.e. proportion at X = 1).

Using the option with low odds ratios as indicated in Hsieh's study[229], $P_1 = 0.2$ and $P_2 = 0.5$. Substituting the above values in the formula will give:

$$n < \frac{4(0.5)(1 - 0.5)\,(7.84)}{(0.2 - 0.5)^2} = 87.1$$

Therefore the number of subjects needed in the study is 87. In the multivariate analysis in this study, several covariates were included in the regression model. However, a study indicated that the number of covariates in a model does not influence the sample size[230].
Given the fact that there were not sufficient children in the 2 clinics, the target sample size for this study could not be attained. In addition, these clinics are the only outpatient centres for children living with diabetes in the North West Region. Therefore, all the 76 children and adolescents who were available at both clinics were recruited into the study after obtaining written informed consent and assent from the parent/guardian and those above 10 years of age respectively.

2.4. Data collection/ equipment.

2.4.1. Structured questionnaire.

The data used in this study was collected using a structured questionnaire (Appendix 1), which was piloted before the study. During a regularly scheduled clinic visit the research staff (LLN) (assisted by a nurse in each clinic) met with each child/adolescent and parent or caregiver and jointly completed the questionnaire for children less than 10 years. For those older than 10 years, the section on the questionnaire addressing knowledge on diabetes was administered separately to the child. The questionnaire was translated from English to French and back translated from French to English, and it contained the following sections: sociodemographic and background characteristics; knowledge of diabetes for children/adolescents and caregivers; diabetes related practices; impact of type 1 diabetes on daily life of these children as well as insulin availability.
Sociodemographic and background information: This section included; age, gender, age at onset of type 1 diabetes, diabetes duration, insulin regimen, primary caregiver and caregiver's level of education, family living arrangements, socioeconomic status, degree of

urbanization, family history of diabetes, health status at time of diagnosis and infections before diagnosis.

- Age and diabetes duration were calculated from the date of birth and date of diagnosis of the disease.
- In a household the primary caregiver was defined as the person in the family most involved in the care of the diabetic child.
- Family living arrangement was categorized as follows; living with both parents, living with a single parent, living with a sibling and living with a family relative or an orphan.
- Degree of urbanization was defined by the area of resident of the patient as follows; urban and rural.
- Health status at time of diagnosis and infections before diagnosis were assessed by asking specific questions on the type of illnesses the child/adolescent suffered from before diagnosis.
- Positive family history of diabetes was defined as having an immediate relative (i.e. of the first degree) with type 1 diabetes.
- Socioeconomic status (SES): This was assessed using the Cameroon public service system of occupation classification and the civil servant categories A, B, and C were used to categorize patients into high, middle and low SES respectively[231]. Individuals not working in the public sector were also assigned to these categories based on their income or profession. This information was provided by the parents/caregivers of the patients. Each child was assigned to a socioeconomic status category based on the highest level of SES of either parent. Furthermore, parental level of education was also assessed as a measure of SES using the questionnaire and four categories were established: no formal education (no elementary education), primary (1 – 6 years of education), secondary (7 – 13 years of education) and higher education (greater than 13 years of education).

Diabetes knowledge of children and adolescents and caregivers: This was assessed using the Michigan Diabetes Research and Training Center's brief diabetes knowledge test[232]. This is a multiple choice questionnaire that was modified to be applicable to the Cameroon patient population. Out of the 23 questions, a total of 15 questions were used since the other 8 were not applicable to our patient population and the results were scored based on the percentage of correct responses.

Diabetes related practices: These included; insulin adherence, dietary adherence, blood glucose monitoring (BGM) adherence, family involvement in diabetes related activities (insulin injection and blood glucose monitoring), regularity of clinic visits and the method of insulin storage.

Diabetes-related practices were self-reported by parents and/or children on the questionnaires.

- **Insulin adherence**: Patient adherence to insulin was determined by the number of doses of insulin missed in the last one week before the study and it was graded as good – for those who never missed any dose, average – for those who missed 1 to 3 doses in the last one week and poor – for those who missed more than 3 doses in the last one week. In addition, reasons for missing the insulin doses were recorded.

- **Dietary adherence**: Patient adherence to diet was evaluated using a 24-hour dietary recall[233] and it was graded using a score derived from the dietary guidelines given at the clinic based on meal frequency and meal content as follows:

Component	Score
Meal frequency	
• 3 meals and 3 snacks or 3 meals and 2 snacks	4
• 3 meals and 1 snack	3
• 3 meals only	2
• Less than 3 meals	1
Meal content (lunch and dinner) – each meal was scored separately and divided by 2.	
• All the components (i.e. containing proteins, carbohydrates and vegetables)	4
• Containing carbohydrates and vegetables	3
• Containing carbohydrates and proteins	2
• Containing only carbohydrates	1
Contra-indicated foods: each time a forbidden food was consumed	-1

In the scoring process of meal content, each time a contra-indicated food (such as soft drinks, added sugar, animal fat) was consumed it was given a score of - 1. A maximum score of 8 was obtained for dietary adherence; a score of less than 4, between 4 and 6, and greater than 6 were interpreted as poor, average and good respectively.

- **Blood glucose monitoring (BGM) adherence**: This was classified according to Hood *et al.*[121] and graded as good – for those who measured their blood glucose 3 or more times a day, average – for those who measured their blood glucose 1 – 2 times a day, and poor – for those who measured their blood glucose less than once a day.
- **Family involvement in diabetes related activities**: This was assessed by the degree of involvement of parents/caregivers in the administration of insulin and BGM. This was then graded as minimal, moderate and maximal involvement using a modified scale used in the study by Anderson *et al.*[207].

Caregiver involvement in insulin injections was determined by the number of doses of insulin injections injected or supervised by the caregiver in the last 24 hours and it was graded as minimal - no caregiver participation, moderate - caregiver injected/supervised only half of the injections and maximal- caregiver gave all the injections.
Also, caregiver involvement in BGM was determined by the degree of participation of the caregiver in the task of BGM was graded as minimal - no caregiver participation, moderate – caregiver reminded the child to check blood glucose, asked the child about the blood glucose level or entered the glucose level in the diary and maximal – caregiver sets up the meter or did the finger prick and registered the results in the diary.

- Regularity of clinic visits was determined by the number of times the patient had attended the outpatient diabetic clinic in the last 6 months before the study.
- Method of insulin storage in the last 3 months prior to the study was classified as refrigeration, a pot of sand/charcoal/cold water or storage at room temperature.

Availability of insulin: This was evaluated by determining the frequency at which the patient has missed insulin supplies from the clinic in the last 3 months prior to the study and was then classified as: never missed, missed every month or once or twice in 3 months. In addition, the ability of the patients to purchase insulin in case it was not available at the clinic was also determined.

Impact of type 1 diabetes on daily life: This was assessed by specific questions on diet restriction, cessation of school or missed school days, poor performance in school, depressed mood, social isolation, hindrance to participate in sports activities and positive impact. There was also free conversation with the patients and parent/caregiver in order to find out other impacts type 1 diabetes was having on the daily life of the children/adolescents.

2.4.2. Data collection forms.

The prospective registration of clinical and laboratory data at diagnosis as part of the childhood diabetes register in Cameroon had started since 2010. To investigate biochemical as well as clinical characteristics of type 1 diabetes at diagnosis and during the study period

and to determine the potential factors associated with diabetic ketoacidosis (DKA) in newly diagnosed children/adolescents, data collection forms were used. Information at diagnosis on date of birth, date of onset of the disease, family history of disease, circumstances leading to diagnosis, duration (number of days) of symptoms before diagnosis reported by the child/adolescent or observed by the parent, height, weight, blood pressure, blood glycaemia, HbA1c, insulin regimen, clinical evidence of diabetic ketoacidosis (DKA) and urine tests (ketonuria) were obtained from the hospital records of the patients.

Also, data collection forms were used to obtain information on treatment adherence, acute and chronic complications, weight, height, blood pressure, blood glycaemia for the children/adolescents during the study.

Clinical evidence of diabetic ketoacidosis was assessed by the presence or absence of functional signs (symptoms or complaints reported by the patient and/or caregiver) including; fever, weight loss, anorexia, polyuria, polydipsia, difficulty in breathing, diarrhea, nausea, vomiting, lack of energy, abdominal pains and pain or tingling in the lower limbs.

2.4.3. Physical examinations.

Height and weight of children/adolescents: Height and body weight were measured by the clinic nurses ensuring that standard protocols were respected. Height was measured to the nearest 0.1 cm using a portable stadiometer (Seca 213, Germany). The body weight of each patient was measured with the child/adolescent wearing light clothes and no shoes using a digital scale (Omron BF 511, Japan) to the nearest 0.1 kg in order to accurately determine the insulin dose per kilogram body weight. The body mass index (BMI) of each participant was then calculated[234].

2.4.4. Laboratory investigations.

Diagnosis of diabetes was done based on the World Health Organization (WHO) criteria[106]. All clinical/biochemical data at diagnosis and during the study period was collected from the Cameroon childhood hospital records, which included: fasting blood glucose, HbA1c, urine dipstick examinations, systolic and diastolic blood pressure and insulin requirements.

2.4.4.1. Glycosylated haemoglobin (HbA1c).

Glycaemic control was determined by the measurement of glycosylated hemoglobin levels. Its value reflects the average level of blood sugar in the previous 2 – 3 months and the higher the HbA1c level, the higher the blood sugar level. HbA1c levels were determined for all the children who participated in the study since it was part of the routine care in the clinic. HbA1c which was the outcome of interest was measured using a BIO-RAD in2it^{TM} analyzer (UK), which makes use of a BIO-RAD A1c system test cartridge. The blood for this purpose was obtained by a finger prick using a sterile lancet after cleansing the area with 70% alcohol. Using a blood key, about 10 µl of blood was collected from the site of the prick which was then fitted into a BIO-RAD A1c system test cartridge. The cartridge was then placed into the BIO-RAD in2it^{TM} analyzer and the automated results (% HbA1c) were displayed and read from the machine after a processing time of 10 minutes. This test makes use of boronate affinity chromatography to separate the glycosylated fraction of haemoglobin from the non-glycosylated fraction.

Quality control to check the optical and operating system of the analyzer was done once a day before samples were tested using an in2it system check cartridge.

2.4.4.2. Blood glycaemia (fasting blood glucose/ postprandial glucose).

Blood glycaemia (fasting blood glucose and post prandial glucose) levels were measured using Accu-Chek Active Blood Glucose monitoring system (Germany). This is done by pricking the side of a fingertip using a lancing device and applying a drop of blood (1µl) onto the Accu-Chek Active test strip. After inserting the test strip into the glucometer, the automated (blood glucose in mg/dl) results are displayed after a processing time of 10 seconds. Also, this was part of the routine care in the clinic.

2.4.4.3. Blood pressure.

Blood pressure levels (i.e. systolic and diastolic blood pressure) were obtained from the children and adolescents using an automated device (Omron M3, Vietnam). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured two times at a 3 minute interval on the same day and it was part of the routine care in the clinic. The measurements

were taken with the participant sitting in a relaxed position with the arm resting and the palm facing upwards. The average of the 2 measurements was recorded.

2.4.4.4. Urine tests.

Keto-Diabur Test 5000 strips (an Accu-Chek product) were used to screen for the presence of ketones, albumin and glucose in urine. The urine was collected in a clean dry container and after dipping a test strip inside, the results are read after 10 seconds.

2.5. Statistical analysis.

Data analyses was done using SPSS for windows version 20.0. Continuous variables were being tested for normality using the Kolmogorov-Smirnov (*K-S*) test. The anthropometric variables (height, weight and BMI) were standardized for age and gender (Z scores) using the WHO AnthroPlus software. This package uses the WHO 2007 growth reference data[235]. Frequency distribution tables were being used to summarize the diabetes specific variables and sociodemographic characteristics of the children. The mean HbA1c was compared across diabetes specific characteristics and different treatment regimens using a parametric *t*-test. Also, a paired *t*-test was used to compare the differences in means of clinical and biochemical parameters of patients at diagnosis and during the study period. Unequally distributed variables were analyzed using the non-parametric Mann-Whitney *U* test. The association between caregiver involvement in diabetes related tasks and patient adherence was tested using chi square test. In addition, the mean diabetes knowledge score of the children was compared across the different age groups and diabetes duration using one-way analysis of variance test (1-way ANOVA).

The study population was then divided into two groups of glycaemic control as measured by HbA1c (poor glycaemic control, HbA1c > 9.0% and good glycaemic control, HbA1c ≤ 9%)[122]. The frequencies of poor glycaemic control by potential determinants were estimated and this was followed by calculation of odds ratios (OR) using a univariate binary logistic regression analysis. Further, a multivariate binary logistic regression analysis (adjusting for age and gender) using a stepwise forward technique was performed to determine the

independent predictors of glycaemic control using all the variables that were significant in the bivariate analysis. The relationship between HbA1c and the different determinants was demonstrated using binary logistic regression models.

The mean clinical and biochemical characteristics of patients according to metabolic status (with and without DKA) at diagnosis were compared using a parametric *t*-test with unequally distributed parameters analyzed using the Mann-Whitney *U* test. The potential risk factors of DKA were calculated and this was followed by the estimation of their corresponding odds ratios (OR) using binary logistic regression analysis. Multivariate analysis was not carried out due to the fact that there was no significant potential risk factor of DKA in the bivariate analysis.

A *p*-value of 0.05 was considered to be statistical significant.

2.6. Ethical considerations.

Ethical approval was obtained from the National Ethics Committee (NEC) of the Ministry of Public Health, Cameroon and the Cameroon Baptist Convention Health Board (CBCHB). Administrative clearance was obtained from the North West Regional Delegation for Public Health of Cameroon. Hospital clearances were also obtained from the Bamenda Regional Hospital and Banso Baptist Hospital.

In addition, the purpose, study procedure and expected outcomes of this study were explained to the participants and their caregivers before data collection was done. Also, written informed consent was obtained from parents/caregivers and assent from adolescents. In addition, all the data collected from the patients was treated with confidentiality. Further, there was an opt out facility to enable those who were no longer willing to participate in the study to withdraw.

3. RESULTS

3.1. Main characteristics of the study population.

This study included 76 children and adolescents (35 boys and 41 girls) and 73.7% had been living with diabetes for more than 2 years. Gender distribution in the first age tertile was almost equal, while there was unequal distribution of boys and girls in the other age tertiles. Table 3.1 shows the main characteristics of the study population. More than 50% of the study participants were females. The mean age at diabetes diagnosis was 15.1 (95% CI 14.4 – 15.8) years with girls having a slightly higher mean age at diagnosis compared to boys (15.4 ±2.6 vs 14.8 ±3.7 years). However, this was not statistically significant. The mean duration of diabetes for the study population was 3.8 (95% CI 3.1 – 4.5) years. Also, a majority of the study participants were living with both biological parents, had a mother as the primary caregiver and received three or more insulin injections daily. In addition, more than 80% of the patients were of low/middle socioeconomic status with a majority of them from the rural area. In addition, 2 patients said they had visited a herbalist for the treatment of diabetes.

Further, more than 90% of the children and adolescents reported having a concomitant infection such as fever, body weakness or a cold at the time of diagnosis.

From the questionnaire, information on sociodemographic characteristics, SES, caregiver involvement in diabetes related practices, availability of insulin, impact of diabetes on daily life and diabetes knowledge assessment of the children were provided by all study participants giving a response rate of 100%. It is important to point out that 4 children (1 boy and 3 girls) died after data collection.

3 of the children (2 girls and 1 boy) were reported to have died in their sleep and were suspected to have died after experiencing hypoglycaemic episodes in the night. In spite of the fact that these children tried to properly manage their blood sugar, they were known for having frequent episodes of extremely low blood sugar levels. The death of the other child (a girl) was unclear but she was suspected to have died of diabetic ketoacidosis.

Table 3.1: Descriptive characteristics of the study population, N [% (95% CI)].

Variables	N	Frequency		Mean	(95%CI)
		%	(95%CI)		
Age Tertiles				15.1	(14.4 – 15.8)
First tertile (4 – 14 years)	25	32.9	(23.4 – 44.1)		
Second tertile (15 – 16 years)	25	32.9	(23.4 – 44.1)		
Third tertile (> 16 years)	26	34.2	(24.5 – 45.4)		
Gender					
Male	35	46.1	(35.3 – 57.2)		
Female	41	53.9	(42.8 – 64.7)		
Body mass index (BMI) (kg/m^2)				23.3	(22.1 – 24.5)
Underweight (< 18.5)	6	7.9	(3.7 – 16.2)		
Normal (18.5 – 25.0)	52	68.4	(53.7 – 77.8)		
Overweight + obese (> 25.0)	18	23.7	(15.5 – 34.4)		
Family structure					
Both parents living together	46	60.5	(49.3 – 70.8)		
Single parent	17	22.4	(14.5 – 32.9)		
Not living with parents	8	10.5	(5.4 – 19.4)		
Orphan	5	6.6	(2.8 – 14.5)		
Primary caregiver					
Mother	45	59.2	(48.0 – 69.6)		
Father	10	13.2	(7.3 – 22.6)		
Sibling	9	11.8	(6.4 – 21.0)		
Other	12	15.8	(9.3 – 25.6)		
Caregiver education					
No formal education	16	21.1	(13.4 – 31.5)		
Primary school	20	26.3	(17.7 – 37.2)		
Secondary/High school	29	38.2	(28.1 – 49.4)		
University	11	14.4	(8.3 – 24.1)		
Duration of diabetes (years)				3.8	(3.1 – 4.5)
< 2	20	26.3	(17.7 – 37.2)		
2 – 5	37	48.7	(37.8 – 59.7)		
> 5	19	25.0	(23.4 – 44.1)		
Insulin Regimen					
2 daily injection	31	40.8	(30.4 – 52.0)		
Multiple daily injection	45	59.2	(48.0 – 69.6)		
Degree of urbanization					
Urban	30	39.5	(29.3 – 50.7)		
Rural	46	60.5	(49.3 – 70.8)		
Socioeconomic status					
Low	53	69.7	(58.7 – 78.9)		
Middle	9	11.8	(6.4 – 21.0)		
High	14	18.4	(11.3 – 28.6)		

CI; confidence interval

In our study population, storage of insulin by patients was done by refrigeration (18.4%), a pot of charcoal/sand or cold water (51.3%) and the rest at room temperature (30.3%). However, glycaemic control in the group which stored insulin in a fridge (9.8%, 95% CI 8.1 – 11.4) was not significantly different from those who stored their insulin in a pot of charcoal/sand or cold water (10.8%, 95% CI 9.9 – 11.8) (p = 0.265). Also, those patients who stored their insulin in a fridge appeared to have similar glycaemic control to those who stored their insulin at room temperature.

Insulin was available to all the children and adolescents at the clinic through the CDiC program. Nonetheless, 14.5% of children and adolescents reported having missed their supply of insulin from the clinic at least once in the previous three months prior to the study. Also, 11.8% said they will be able to purchase insulin in case there was a delay in supply by the clinic.

3.2. Clinical and biochemical characteristics at diagnosis and during the study period.

Table 3.2 presents the differences in clinical and biochemical parameters of the study participants at diagnosis and during the study period. There was a significant decrease in HbA1c from diagnosis (11.1%) to the study period (10.3%) (p = 0.011). 2.6% of the patients during the study period had a postprandial glucose level of > 600 mg/dl compared to 7.9% at diagnosis. However, no statistical significant difference was observed in the mean fasting blood glucose and mean diastolic blood pressure.

Table 3.2: Differences in clinical and biochemical parameters at diagnosis and during the study period.

Variables	At diagnosis		Study Period		*p*-value*
	Mean	(95%CI)	Mean	(95%CI)	
Age (years)	15.1	(14.4 – 15.8)	18.9	(18.4 – 19.4)	< 0.001
Body mass index (kg/m^2)	22.9	(21.5 – 24.3)	23.3	(22.1 – 24.5)	0.408
BMI SDS$^+$	0.57	(-0.04 – 1.18)	0.29	(-0.07 – 0.65)	0.359
Systolic blood pressure (mmHg)	112.7	(109.8 – 115.6)	116.9	(113.9 – 119.9)	0.021
Diastolic blood pressure (mmHg)	68.4	(66.1 – 70.7)	70.8	(68.5 – 73.1)	0.079
HbA1c (%)	11.1	(10.5 – 11.7)	10.3	(9.6 – 10.9)	0.011
Fasting blood glucose (mg/dl)	184.2	(151.3 – 217.1)	169.8	(136.1 – 203.5)	0.493
Post prandial glucose (mg/dl)	364.4	(330.8 – 398.0)	266.9	(236.1 – 297.8)	< 0.001

CI; confidence interval: *calculated using paired *t*-test. . $^+$Based on WHO 2007 reference data. Mean height, weight and BMI SDSs included only children ≤ 19 years (n = 41).

It is shown in table 3.3 that during the study period, children and adolescents in the third age tertile had a slightly lower mean HbA1c (9.8%, 95% CI, 9.1 – 10.5) compared to those in the first age tertile (10.8%, 95% CI, 10.2 – 11.4, p = 0.209). However, there was no significant linear trend for HbA1c to decrease with increasing age (p = 0.228). Also, there was no significant difference in the glycaemic control between boys and girls in the different age tertiles.

Table 3.3: Differences in clinical and biochemical data by age groups during the study period, [mean (95% CI)].

Variables	Age tertiles			*p*-value*
	First Mean (95% CI)	Second Mean (95% CI)	Third Mean (95% CI)	
Weight (kg)	56.5 (54.1 – 58.9)	61.3 (57.4 – 65.2)	67.4 (64.0 – 70.8)	0.029
Weight SDS^{+}	-0.50 (-1.00 – 0.00)	-0.88 (-1.95 – 1.90)	0.35 (-0.83 – 1.53)	0.146
Height (cm)	159.1 (157.2 – 160.9)	160.6 (158.7 – 162.5)	166.1 (163.9 – 168.2)	0.073
Height SDS^{+}	-1.04 (-1.54 – -0.55)	-1.60 (-2.48 – -0.73)	-0.36 (-1.31 – 0.60)	0.072
Body mass index (kg/m^2)	21.7 (21.0 – 22.4)	23.9 (22.2 – 25.6)	24.3 (23.3 – 25.3)	0.165
BMI SDS^{+}	0.14 (-0.37 – 0.64)	0.23 (-0.44 – 0.90)	0.65 (-0.33 – 1.64)	0.514
Systolic BP(mmHg)	117.5 (114.5 – 120.5)	117.1 (113.8 – 120.4)	116.9 (114.4 – 119.4)	0.985
Diastolic BP (mmHg)	72.0 (69.4 – 74.6)	71.4 (69.2 – 73.6)	69.5 (67.5 – 71.5)	0.645
HbA1c (%)	10.8 (10.2 – 11.4)	10.3 (9.6 – 11.0)	9.8 (9.1 – 10.5)	0.482
Fasting blood glucose (mg/dl)	159.8 (134.7 – 184.8)	164.4 (137.4 – 191.4)	145.7 (127.1 – 164.3)	0.820
Postprandial glucose (mg/dl)	268.3 (239.3 – 297.3)	251.8 (222.6 – 280.9)	277.9 (250.6 – 305.1)	0.760

*calculated using one way ANOVA $^{+}$Based on WHO 2007 reference data. Mean height, weight and BMI SDSs included only children ≤ 19 years (n = 41).

The distribution of clinical symptoms reported by the patient or caregiver before diagnosis is shown in Figure 3.1. The most frequent symptom reported was polyuria and polydipsia and it was present in 63.2% of the study population. 13.2 % were reported to have coma or impaired consciousness during diagnosis, while 2.6% had weight loss. This figure shows that among type 1 diabetic children and adolescents in the North West Region of Cameroon, the frequency of polyuria and polydipsia outweighs the other clinical symptoms. Also, the mean duration of symptoms before diagnosis was 34.4 ± 28.5 days. 17.1% of the study

population had symptoms over 2 months, meanwhile 5.3% had duration of symptoms of ≤ 7 days.

In addition, ketonuria was found in 18.4% of the children during diagnosis. 24.2% of boys presented with ketonuria at diagnosis compared to 18.7% of girls. Nevertheless, urine analysis at diagnosis was done only for 85.5% of the study population (33 boys and 32 girls).

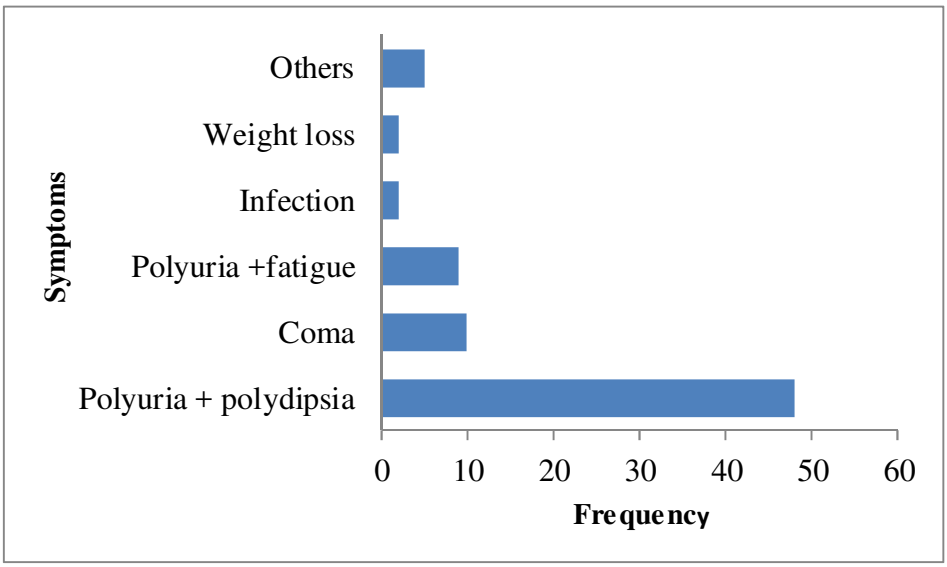

Figure 3.1: Clinical symptoms reported before diagnosis of type 1 diabetes.

Less than 40% and 18.4% of the study population reported a positive family history of diabetes and hypertension respectively. Nevertheless, a positive family history of diabetes or hypertension did not influence glycaemic control in the children. Also, more than 40% of the children had not been hospitalized in the last 12 months prior to the study. In addition, 28.9% were found to have experienced hypoglycaemic episodes in the last 3 months before the study with less than 4% of them being severe. In addition, more than 90% of the study population never had ketoacidosis in the last 12 months prior to the study.

The percentage of children reported to be suffering from diabetes complications such as foot ulcers, retinopathy and neuropathy was 2.6%, 7.9% and 1.3% respectively. That notwithstanding, there was no other chronic complication reported among the children.

3.3. Comparison of clinical and biochemical characteristics of the study population according to gender.

Table 3.4 depicts the differences in the biochemical and the clinical characteristics of the study population at diagnosis and during the study period by gender. There was no statistically significant difference observed in most of the clinical and biochemical parameters of the investigated population according to gender during the study period. However, the mean postprandial blood glucose level during the study period was observed to increase with increasing age in boys, a finding which was not found in girls. Nevertheless, it was not significant. Also, after adjusting for age, there was a significant difference in BMI SDS between boys and girls during the study period and its calculation was done only for 45.7% of boys and 60.9% of girls.

Table 3.4: Differences in biochemical and clinical parameters at diagnosis and study period by gender, [mean (95% CI)].

Variables	Boys N = 35		Girls N = 41		*P**-value
	Mean	(95%CI)	Mean	(95%CI)	
At diagnosis					
Age (years)	14.8	(13.5 – 16.1)	15.4	(14.6 – 16.2)	0.417
Body mass index (kg/m^2)	21.2	(19.5 – 22.9)	24.2	(22.1 – 26.3)	0.033
BMI SDS$^+$	0.40	(-0.12 – 0.92)	0.90	(0.35 – 1.45)	0.183
Systolic blood pressure (mmHg)	113.6	(108.9 – 118.2)	111.9	(108.1 – 115.7)	0.575
Diastolic blood pressure (mmHg)	67.9	(63.9 – 71.8)	68.7	(66.1 – 71.3)	0.730
HbA1c (%)	11.4	(10.4 – 12.4)	10.9	(10.1 – 11.7)	0.409
Fasting blood glucose (mg/dl)	192.6	(136.5 – 246.7)	174.8	(138.4 – 211.2)	0.566
Post prandial glucose (mg/dl)	411.3	(359.3 – 463.3)	329.3	(289.6 – 369.0)	0.013
During study period					
Age (years)	19.3	(18.6 – 19.9)	18.7	(17.9 – 19.4)	0.237
Body mass index (kg/m^2)	22.0	(20.8 – 23.2)	24.4	(22.4 – 26.4)	0.050
BMI SDS$^+$	-0.18	(-0.65 – 0.29)	0.60	(0.11 – 1.09)	0.021
Systolic blood pressure (mmHg)	118.5	(113.9 – 123.1)	116.1	(112.3 – 119.7)	0.410
Diastolic blood pressure (mmHg)	71.8	(68.2 – 75.4)	70.3	(67.5 – 73.1)	0.517
HbA1c (%)	10.8	(9.7 – 11.9)	9.9	(9.0 – 10.8)	0.228
Fasting blood glucose (mg/dl)	153.5	(126.2 – 180.8)	160.1	(125.6 – 194.6)	0.791
Post prandial glucose (mg/dl)	274.3	(232.3 – 316.3)	260.2	(222.2 – 298.2)	0.620
Diabetes duration (years)	4.5	(3.2 – 5.8)	3.3	(2.5 – 4.1)	0.130

CI; confidence interval, $^*p$-value calculated using independent *t*-test; HbA1c, glycosylated haemoglobin.
$^+$Based on WHO 2007 reference data. Mean BMI SDS during study period included only participants ≤ 19 years (16 boys and 25 girls).

3.4. Glycosylated haemoglobin (HbA1c) by diabetes specific characteristics.

The mean HbA1c of the study population was 10.3 ± 2.9% and only 23.7% of the children attained the ADA HbA1c target level of < 7.5%. In addition, 17.1 % of children/adolescents had mean HbA1c of ≥ 14%. These findings confirm the fact that a majority of the children and adolescents in sub- Saharan Africa with type 1 diabetes are not adequately controlled.

Girls on average had a lower mean HbA1c (9.9 %, 95% CI 9.0 – 10.8) compared to boys (10.8%, 95% CI 9.7 – 11.9). However, this was not significant. Table 3.5 shows the diabetes-related characteristics by glycaemic control of the patients.

Glycaemic control (HbA1c) was more likely to be better among children having a mother as a primary caregiver (8.7%, 95% CI 8.0 – 9.4) compared to those having a father, a sibling or another family member as caregiver (12.7%, 95% CI 11.9 – 13.4). Also, there was no significant difference in glycaemic control between the different categories of diabetes duration, family living arrangements, patient's educational level and family history of diabetes ($p > 0.05$).

It was observed that 62.9% of patients being treated on 2 daily insulin injections had good glycaemic control compared to 37.1% of those on multiple daily insulin injections. In addition, more than 80% of the study participants who checked their blood glucose 3 or more times a day had good glycaemic control compared to 17.1% of those who had 2 or less blood glucose checks a day. Further, 58.3% of children with poor glycaemic control had a positive family history of diabetes.

Table 3.5: HbA1c of patients by specific diabetes characteristics, [mean (95% CI)].

Variable	HbA1c		*p*-value*
	Mean	95%CI	
Age tertiles			
First	10.8	(10.2 – 11.4)	
Second	10.3	(9.6 – 11.0)	0.561
First	10.8	(10.2 – 11.4)	
Third	9.8	(9.1 – 10.5)	0.209
Duration of diabetes (years)			
< 2	10.5	(9.1 – 11.9)	
2 – 5	10.1	(9.1 – 11.1)	0.630
< 2	10.5	(9.1 – 11.9)	
> 5	10.5	(9.2 – 11.8)	0.924
Insulin Regimen			
2 daily injections	8.9	(7.9 – 9.9)	
Multiple daily injection	11.2	(10.4 – 12.0)	0.001
Family structure			
Both parents living together	10.2	(9.3 – 11.1)	
Others	10.4	(9.3 – 11.5)	0.771
Primary caregiver			
Mother	8.7	(8.0 – 9.4)	
Others	12.7	(11.9 – 13.4)	< 0.001
Caregiver education			
None/primary	9.9	(8.9 – 10.8)	
Secondary/tertiary	10.7	(9.7 – 11.7)	0.273
Clinic visits in the last 6 months			
1 – 3 times	11.5	(10.7 – 12.3)	
> 3 times	8.7	(7.8 – 9.6)	< 0.001
Family history of diabetes			
Positive family history	10.5	(9.1 – 11.9)	
No family history	10.2	(9.4 – 11.0)	0.654

* Calculated using students' independent *t*-test; CI confidence interval

The mean diabetes knowledge score for adolescents was 65.4 ± 14.4% and it revealed an increasing linear trend with increasing diabetes duration. That notwithstanding, it was not significant. The results of diabetes knowledge assessment of adolescents are summarized on Table 3.6. Also, the adolescent's level of education had an influence on the diabetes knowledge score. Adolescents with no formal education as well as school dropouts had a lower mean score for the diabetes knowledge test compared to those who had attained a

certain level of education that was adequate for their age. In addition, all the adolescents had knowledge of the importance of HbA1c in the management of T1D. Nevertheless, knowledge of HbA1c did not influence glycaemic control.

Table 3.6: Diabetes knowledge scores of adolescents with type 1 diabetes.

Diabetes characteristics	Score		*p*-value*
	Mean (%)	95%CI	
Age tertiles			
First	65.9	(62.1 – 69.7)	0.367
Second	62.2	(59.1 – 65.3)	
Third	67.9	(64.9 – 70.8)	
Duration of diabetes			
< 2 years	59.2	(51.6 – 66.7)	0.079
2 to 5 years	67.5	(63.5 – 71.6)	
> 5 years	67.7	(60.1 – 75.2)	

* Calculated using one way ANOVA

3.5. Adherence to the different treatment regimens and caregiver involvement in diabetes related tasks

Figure 3.2 indicates the frequency of adherence to the different treatment regimens. Insulin adherence was good in less than 40% of the study population while poor adherence was observed in 22.4% of the study population. Also, adherence to BGM was good in more than half of the study participants. Adherence to the dietary regimen prescribed at the clinic was average in a majority (81.6%) of the patients. Also, it was realized that most adolescents had difficulties reducing the quantity of carbohydrates in the diet.

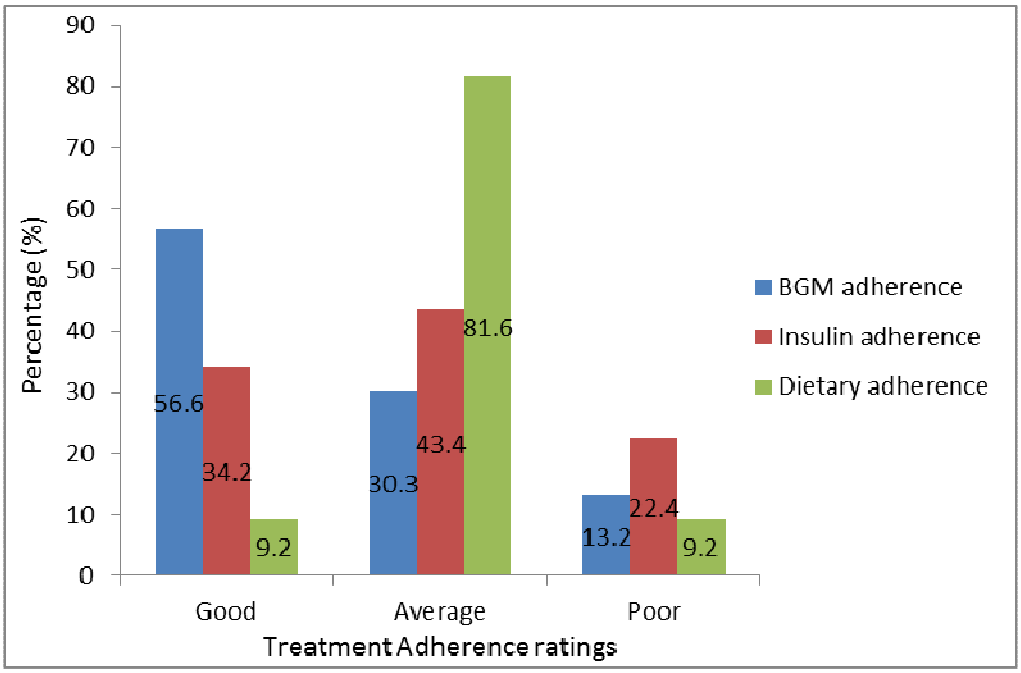

Figure 3.2: Treatment adherence in children and adolescents with type 1 diabetes.

Table 3.7a shows adherence to the different treatment regimens by age tertiles. There was a significant association between BGM adherence by age tertiles (Chi-square value = 10.4, df = 4, p = 0.034), a finding that was not observed with insulin and dietary adherence.

Table 3.7a: Adherence to the different treatment regimens by age tertiles.

	First tertile N = 25		Second tertile N = 25		Third tertile N = 26		Total N = 76		*p*-value*
	N	(%)	n	(%)	n	(%)	n	(%)	
Insulin									
Good	8	32	11	44	7	26.9	26	34.2	0.324
Average	9	36	9	36	15	57.7	33	43.4	
Poor	8	32	5	20	4	15.4	17	22.4	
Diet									
Good	2	8	3	12	2	7.7	7	9.2	0.966
Average	21	84	20	80	21	80.8	62	81.6	
Poor	2	8	2	8	3	11.5	7	9.2	
BGM									
Good	18	72	14	56	11	42.3	43	56.6	0.034
Average	5	20	5	20	13	50	23	30.3	
Poor	2	8	6	24	2	7.7	10	13.1	

* Calculated using Chi square

Table 3.7b shows the differences in mean HbA1c by adherence to the different treatment regimens. Glycaemic control was significantly improved among children who had good adherence to insulin and BGM ($p < 0.001$). Also, the insulin regimen used (whether 2 daily insulin injections or multiple daily injections) by the children and adolescents did not have an effect on adherence ($p > 0.05$).

Table 3.7b: Differences in treatment adherence and glycaemic control.

Treatment adherence	Mean HbA1c (95% CI)				*p*-value*
	Good		Poor/Average		
Diet	11.0	(8.6 – 13.4)	10.2	(9.5 – 10.9)	0.506
BGM	8.8	(7.9 – 9.6)	12.2	(11.5 – 12.9)	< 0.001
Insulin	8.8	(7.6 – 9.9)	11.1	(10.3 – 11.9)	0.001

*Calculated using independent *t*-test.

In addition, in this study it was observed that caregiver involvement in the diabetes-related tasks of the child varied with the type of task (Tables 3.8a and 3.8b). Maximal parental involvement in the task of BGM was observed in 88.4% of the children compared to 57.7%

in the task of insulin injection. Table 3.8a demonstrates that maximal caregiver involvement in the task of BGM was significantly associated with good patient adherence to BGM (Chi-square = 44.5; df = 2; $p < 0.001$). However, no such relationship was observed in the task of insulin injection as indicated in Table 3.8b.

Table 3.8a: Association between caregiver involvement in BGM and patient adherence to BGM.

Involvement	Adherence ratings				Total		*p*-value*
	Good N = 43	(%)	Poor/Average N = 33	(%)	N = 76	(%)	
BGM							
Minimal	1	2.3	13	39.4	14	18.4	< 0.001
Moderate	4	9.3	16	48.5	20	26.3	
Maximal	38	88.4	4	12.1	42	55.3	

*Calculated using Chi square test

Table 3.8b: Association between caregiver involvement in insulin injection and patient adherence to insulin injection.

Involvement	Adherence ratings				Total		*p*-value*
	Good N = 26	(%)	Poor/Average N = 50	(%)	N = 76	(%)	
Insulin injection							
Minimal	9	34.6	13	26.0	22	29.0	0.161
Moderate	2	7.7	13	26.0	15	19.7	
Maximal	15	57.7	24	48.0	39	51.3	

*Calculated using Chi square test

Among children in the first age tertile, 68% of caregivers had maximal involvement in BGM compared to 46.2% among those in the third age tertile ($p = 0.270$). Equivalent findings were also observed in the task of insulin injection, 52% versus 46.2% ($p = 0.778$) for those in the first and third age tertiles respectively.

3.6. Clinical and biochemical characteristics of patients according to metabolic status at diagnosis of type 1 diabetes.

Table 3.9 shows the clinical and laboratory data of children according to metabolic status at diagnosis of type 1 diabetes. At diagnosis less than 30% of the children and adolescents had evidence of diabetic ketoacidosis (DKA) with a decreasing frequency with increasing age in males but not with females. On average more girls (34.1%) than boys (22.8%) presented with ketoacidosis at diagnosis. Nevertheless, the frequency of diabetic ketoacidosis was found to be almost the same among children and adolescents in all age tertiles.

Table 3.9: Comparison of clinical and laboratory data of children according to metabolic status at diagnosis of type 1 diabetes.

Clinical characteristic	DKA N= 22		No DKA N= 54		*p*-value
	Mean	95%CI	Mean	95%CI	
Age (years)	15.1	(13.9 – 16.3)	15.2	(14.3 – 16.1)	0.898*
Duration of symptoms (days)	45.2	(24.0 – 66.4)	30.1	(24.2 – 35.9)	0.163**
Postprandial blood glucose (mg/dl)	388.2	(333.4 – 443.0)	354.4	(312.6 – 396.2)	0.359*
Fasting blood glucose(mg/dl)	209.0	(149.4 – 268.6)	170.3	(145.4 – 195.2)	0.241*
$HbA1_C$ at diagnosis (%)	12.1	(10.8 – 13.4)	10.7	(9.9 – 11.4)	0.045**
BMI at diagnosis (kg/m^2)	20.4	(18.7 – 22.1)	23.9	(22.1 – 25.7)	0.016*

* Calculated using independent *t*-test: **calculated using Mann-Whitney U test: CI; Confidence interval; DKA, Diabetic ketoacidosis

3.7. The impact of type 1 diabetes on the daily life of children and adolescents

Type 1 diabetes had different impacts on the daily life of children and adolescents. More than 60% reported that diabetes had an impact on their lives (Table 3.10). 3.9% of the children reported a positive impact on their daily life by making them more responsible while 72.4% said the disease had a negative impact on their life. This was much higher among adolescents > 15 years with more girls (68.4%) reporting negative impact compared to boys (48.8%). Dietary difficulties and poor school performance were the most common problems reported by the patients. There was no statistically significant difference in glycaemic control among children who reported a negative impact on their lives and those who had no impact.

Table 3.10: Impact of type 1 diabetes on daily life of children and adolescents.

Impact	N	%	Mean HbA1c (%)		
			Negative impact	No impact	*p*-value*
Sports restriction	30	39.5	10.7	10.0	0.367
Social isolation	30	39.5	10.4	10.2	0.759
Unhappy mood	37	48.7	10.5	10.1	0.513
Diet restriction	60	78.9	10.4	10.0	0.644
Poor school performance	37	48.7	10.2	10.4	0.744
Positive impact	3	3.9	-	-	-

*Calculated using independent *t*-test

3.8. Bivariate and multivariate analysis.

Bivariate analysis (unadjusted associations between poor glycaemic control and individual factors) in Table 3.11a indicated that having a mother as the primary caregiver (OR 0.07, 95% CI, 0.02 – 0.2), being on 2 daily insulin injections (OR 0.2, 95% CI, 0.1 – 0.5), good adherence to blood glucose monitoring (OR 0.1, 95% CI, 0.04 – 0.3) and good adherence to insulin injection (OR 0.3, 95% CI, 0.1 – 0.8) were significantly ($p < 0.05$) associated with good glucose control as indicated by HbA1c, while age (OR 1.1, 95% CI 0.4 – 3.2), diabetes duration (OR 0.9, 95% CI 0.3 – 2.9) and socioeconomic status (OR 2.4, 95% CI 0.9 – 6.5) did not show any significant association ($p > 0.05$) with glycaemic control.

Table 3.11a: Frequency and odds ratio for the association between poor glycaemic control and determinants (bivariate analysis).

Determinants	N	Poor glycaemic control			*p*-value
		Frequency	OR	95% CI	
Age tertiles					
Third (> 16 years)	26	50.0	1.1	(0.4 – 3.2)	0.886
Second (15 – 16 years)	25	52.0	1.5	(0.5 – 4.5)	0.474
First (4 – 14 years)	25	60.0	ref		
Diabetes duration (years)					
>5	19	52.6	0.9	(0.3 – 2.9)	0.928
2 - 5	37	51.4	1.4	(0.4 – 4.8)	0. 643
< 2	20	60.0	ref		
Primary caregiver					
Mothers	45	31.1	0.07	(0.02 – 0.2)	< 0.001
Others	31	87.1	ref		
Insulin regimen					
2 daily injection	45	21.9	0.2	(0.1 – 0.5)	< 0.001
Multiple daily injection	31	71.1	ref		
Insulin adherence					
Good	26	34.6	0.3	(0.1 – 0.8)	0.017
Poor/average	50	64.0	ref		
BGM adherence					
Good	43	32.6	0.1	(0.04 – 0.3)	< 0.001
Poor/average	33	81.8	ref		
Dietary adherence					
Poor/average	69	52.2	2.3	(0.4 – 12.6)	0.341
Good	7	71.4	ref		
Caregiver involvement in insulin injection					
Minimal/moderate	37	83.8	14.9	(4.8 – 46.5)	< 0.001
Maximal	39	25.6	ref		
Caregiver involvement in BGM					
Minimal/moderate	34	79.4	7.7	(2.7 – 22.0)	< 0.001
Maximal	42	33.3	ref		
Clinic visits in the last 6 months					
1 – 3 times	44	70.5	5.2	(1.9 – 14.1)	0.001
> 3 times	32	31.3	ref.		
Socioeconomic status					
Low/middle	53	60.4	2.4	(0.9 – 6.5)	0.091
High	23	39.1	ref.		
Degree of urbanization					
Rural	46	60.0	1.5	(0.6 – 3.8)	0.394
Urban	30	50.0	ref.		

OR; odds ratio (unadjusted for age and gender): CI; confidence interval: BGM; blood glucose monitoring: Poor glycaemic control; HbA1c > 9.0%

Table 3.11b shows the results of the multivariate analysis which included only variables that were significant in the bivariate analysis. Multivariate analysis showed that having a mother as the primary caregiver (OR 0.02, 95% CI 0.002 - 0.189, $p < 0.001$) was significantly associated with good glucose control. Also, participants who had minimal/moderate caregiver involvement in the task of insulin injection had an increased risk of poor glucose control (OR 26.8, 95% CI 4.4 – 56.1, $p < 0.001$).

Table 3.11b: Multivariate binary logistic regression analysis with HbA1c (%) as dependent variable, (odds ratios adjusted for age and gender).

	B	Standard error	Odds ratio (OR)	(95% CI)	*p*-value
Primary caregiver	-3.436	1.082			
Mother			0.02	(0.002 – 0.189)	0.001
Others				ref.	
Caregiver involvement in insulin injection	3.617	1.046			
Minimal/Moderate			26.8	(4.4 – 56.1)	0.001
Optimal				ref.	
Constant	1.795	1.557			

OR; odds ratio: CI; confidence interval

Also, the results of the bivariate analysis to determine the risk factors for DKA at diagnosis demonstrated that the presence of ketonuria at diagnosis (OR 1.9, 95% CI 0.5 – 7.9), age (OR 0.8, 95% CI 0.2 – 2.6) and a positive family history of diabetes at diagnosis (OR 0.9, 95% CI 0.3 – 2.9) did not show a significant association with DKA as shown on Table 3.11c.

Table 3.11c: Frequency and odds ratio for the association between diabetic ketoacidosis and potential risk factors (bivariate analysis).

Determinants	N	Diabetic ketoacidosis			*p*-value
		Frequency	OR	95%CI	
Age					
First tertile	25	28.0	0.8	(0.2 – 2.6)	0.691
Second tertile	25	32.0	0.9	(0.3 – 3.2)	0.931
Third tertile	26	26.9	ref		
HbA1c					
Poor outcome	41	59.1	1.3	(0.5 – 3.7)	0.566
Good outcome	35	40.9	ref		
Ketonuria					
Yes	14	21.4	1.9	(0.5 – 7.9)	0.353
No	52	36.5	ref		
Missing data	10				
Positive family history of diabetes					
Yes	24	29.2	0.9	(0.3 – 2.9)	0.997
No	52	28.8	ref		

OR; odds ratio (adjusted for age and gender): CI; confidence interval. Ketonuria was done only for 65 children (33 boys and 32 girls).

.

4. DISCUSSION

4.1. Relationship between sociodemographic and diabetes related characteristics with glycaemic control.

Achieving good glycaemic control is the cornerstone in the management of type 1 diabetes as it is essential for preventing short-term and long-term complications. However, the management of T1D in children and adolescents remains a challenge to the patient, their families and the healthcare provider. Current standards for management of the disease focus on optimizing glycaemic control in order to reduce the risks of short-term and long-term complications.

This study sets out to identify the factors that predict good glucose control in children with type 1 diabetes in the North West Region of Cameroon. This study has demonstrated that having a mother as a primary caregiver is an important predictor of good glycaemic control among children with type 1 diabetes. Also, it was confirmed from the multivariate analysis that children with minimal/moderate caregiver involvement in the task of insulin injection were at risk of poor glucose control as measured by HbA1c.

Our study found that the mean HbA1c of the study population was 10.3 ± 2.9% and that more than three-quaters (76.3%) of the patients in this study were not adequately controlled (HbA1c
> 7.5%), values similar to those obtained in Tanzania[126] (10.65%), Sudan[128] (9.3%) and Kenya[236] (12.1%) but worse than values observed in the US[199] (7.6%), Denmark[125] (8.20%), Germany and Austria[127] (7.8%) and Germany[203] (8.7%). However, there was a significant decrease in mean HbA1c from the time of diagnosis to the study period which is an indication that the intervention is working to some extent.

Despite the free and regular supply of insulin and blood glucose monitoring equipment to the children and adolescents involved in this study, glycaemic control was still poor. This indicates that there could be other underlying factors that contribute to poor glycaemic control which need to be identified. For instance, a number of factors including irregular

supply of insulin, non-availability of structured diabetes programs, and lack of acceptance of chronic diseases within the society (employer/school) may contribute to this finding.
Also, poor socioeconomic conditions as well as non-compliance to the insulin regimen and diet are likely to play a major role in the poor glycaemic control observed and consequently poor prognosis for the children/adolescents. In addition, there are biological, behavioural and cultural barriers as well as individual/family preferences that affect treatments decisions for the patient. These findings highlight the necessity for more efforts in the management and follow-up of paediatric type 1 diabetics in Cameroon in order to reduce complications resulting from poor glycaemic control.

There are very few studies in Africa which have provided information on glycaemic control. For instance, a study by Pillay *et al.*[237] in South Africa among children aged 6 to 10 years with type 1 diabetes found a mean glycaemic control of 9.7%. Nevertheless, this study included only children six to ten years of age and also had a very small sample size.

It is unclear whether age of the patient and duration of diabetes impact on glucose control. The mean duration of diabetes in our study population was 3.8 ± 3.2 years. Even so, there was no significant difference in glycaemic control in the different categories of diabetes duration, studies carried out in the UK[193] and France[197] indicate that older age and longer duration of diabetes is associated with poor glycaemic control. However, a study by Elbargi *et al.*[128] among insulin dependent type 1 diabetics in Sudan indicated a higher incidence of poor glycaemic control among younger type 1 diabetics. Nevertheless, this study included patients with type 1 diabetes age 6 – 60 years. Age was however not associated with glycaemic control in studies from the US[120], New Zealand[195], Australia[196] and Egypt[202]. This finding is in line with the present study, where no significant association between age or duration of diabetes and glycaemic control was observed.

Poor glycaemic control with increasing age among type 1 diabetics may be attributed to a decrease in treatment compliance, socio-cultural barriers and less parental involvement or supervision in older children. Also, it might be as a result of pubertal hormones from the

rapid biological changes associated with the onset of puberty and psychosocial factors in this age group.

This current study has shown a significant association between primary caregiver involvement and good glycaemic control. This was demonstrated by the significantly lower mean HbA1c (8.7%) in children whose primary caregiver was the mother compared to an HbA1c of 12.7% in those who had a primary caregiver other than the mother. This could be explained by the fact that most often it is the primary responsibility of the mother to care for pediatric patients. It could also be an indication of a proper functioning family structure because in a case of family dysfunction, the diabetic child will be perceived as a burden and this will likely correlate with a higher HbA1c.

The multivariate analysis indicates that mother as the primary caregiver was an important determinant in the diabetes management of children and consequently treatment outcome. Currently, it is unclear whether it is the involvement of the mother herself which is important or whether the fact that the mother is the primary caregiver represents an indicator for a setting where good glucose control can be easily achieved. Nevertheless, in sub-Saharan Africa there is no known study specifically addressing the issue of primary caregiver with respect to the metabolic outcome (as measured by glucose control) in the paediatric population with type 1 diabetes. Several studies have demonstrated a significant association between maternal knowledge and good glucose control among diabetic children whose mothers are the main caregivers. For instance, studies by Al-Odayani *et al.*[214] and Soheilipour *et al.*[219] found that children of mothers with more knowledge of diabetes and better education irrespective of socioeconomic status were better controlled underscoring the importance of the mother's knowledge and level of education in the care of diabetic children. Also, Tahirovic and Toromanovic[217], in a study which investigated the role of mother's diabetes knowledge on glycaemic control in diabetic children in Bosnia and Herzegovin, demonstrated that there was improved glycaemic control among children of mothers with more diabetes knowledge.

Socioeconomic status (SES) has been recognized as an important predictor of type 1 diabetes outcome[190]. In the present study, it was noticed that children from low/middle SES displayed poor glycaemic control. This finding is consistent with that from other studies which have previously shown that low SES was associated with poor glycaemic control among children with type 1 diabetes[195,199,201,238,239]. Similarly, a study by McKinney *et al.*[193] observed that patients from deprived areas had poorer glycaemic control as compared to those from affluent areas. In addition, Overstreet *et al.*[201] in the USA observed that children from lower socioeconomic status were found to have an average glycaemic control which was 2.2% higher than those of middle SES. The relationship between poverty and poor glycaemic control can be explained by the fact that patients from low income backgrounds will be disadvantaged to meet treatment targets due to lack of proper education which is necessary for the management of the disease.

Family living arrangement was not significantly associated with glycaemic control in this study. However, it was an important predictor in other studies[204,240]. For instance a study by Thompson *et al.*[205] found that glycaemic outcomes in children from single mother families had an average HbA1c of 1.2% higher than those from two parent families. The authors attributed this to the fact that single mothers were of a lower income status and had a lower level of education. Equivalent findings have been reported by Araujo and Mazza[241] in Argentina.

Both parents not living together implies that there will be a few people caring for the patient or family dysfunction problems which might affect the ability to provide the support needed for diabetes management and this will have an effect on the glycaemic control of the child.

In this current study, the majority of participants were on multiple daily insulin injections which is the currently recommended mode of treatment for patients with type 1 diabetes. Surprisingly, it was observed that being on twice daily insulin injections was associated with better glucose control than multiple (3 or more) insulin injections. Although this is counterintuitive at first glance it may represent the fact that only children not well controlled were switched to multiple insulin injections as the “default” management is twice daily

insulin injections. Unfortunately, it was not recorded why children were switched to multiple injections.

The storage of insulin did not have an effect on the glycaemic control in our study, although it can play a role in other African countries[126]. Temperatures in the North West Region of Cameroon frequently go above 25^{o}C, as such the temperature in a pot of sand/charcoal or cold water cannot be ascertained. Although insulin can still be left at room temperature for a period of one month and it is still safe to be used, it is difficult to guarantee this aspect in this part of the country. Nevertheless, refrigeration if available still remains the best choice for insulin storage. Data on the temperature inside the pot of sand/charcoal or cold water can be collected and if acceptable, it can be used as an alternative method of storing insulin for patients without fridges.

The number of diabetic clinic visits has been found to be predictive of glycaemic control with irregular clinic attendance being associated with higher levels of HbA1c. Our study found a significant association between the number of visits to the healthcare provider and good glycaemic control. It has been documented that patients who do not come to clinic regularly have difficulties adhering to the different treatment regimens and they have a higher risk of diabetes complications[242]. Frequent visits to the healthcare provider allow for more frequent adjustments of insulin regimens and more educational sessions if necessary. Similarly, most but not all studies have found that more frequent visits to the diabetic clinic resulted in improved glycaemic control[120,126,210,211,212].

Knowledge of diabetes is a key component in the management of type 1 diabetes. Also, education of both the child and caregiver is of critical importance in ensuring adherence of the complex tasks involved in effective diabetes management. In this study, the mean diabetes knowledge score for adolescents was 65.4 $\pm$ 14.4%. This is an indication that there is a significant diabetes knowledge deficit among the children. Also, there was no significant association between diabetes knowledge of adolescents and HbA1c. In addition, studies have found that parental diabetes knowledge had an effect on glycaemic control[216, 219]. For

instance, Stallwood *et al.*[218] found that higher parental scores were associated with lower HbA1c levels after using all the questions of the Michigan Diabetes Research and Training Centre's brief diabetes knowledge test to assess parental knowledge of diabetes. There is therefore need to emphasize on the key role of parental diabetes knowledge for better control in children and adolescents. Unfortunately, parental/caregiver diabetes knowledge was not assessed in this study because most parents/caregivers did not complete the section of the questionnaire addressing diabetes knowledge for parents/caregivers.

The limitations of this section are that the cut-off level to define "good" glucose control in this study was arbitrary considering the distribution of the HbA1c values observed in the study population. In addition, given the consistently poor glycaemic control reported in most studies from sub-Saharan Africa[126,128,236], an HbA1c target of ≤ 9.0% slightly above the mean HbA1c levels attained in the developed nations was used in the study. Also, the criteria used to classify participants according to the different socioeconomic backgrounds was the Cameroon public service classification of civil servants, which does not adequately reflect those in the private sector. However, a study in urban Cameroon has shown the World Bank household amenities score to be a better indicator for SES in developing economies[231].

In addition, the lack of association observed between glycaemic control and age, diabetes duration and family living arrangements might be attributed to the small sample size of this study.

4.2. Relationship between caregiver involvement in diabetes management and adherence to the treatment regimen with glycaemic control.

Better treatment outcomes are being observed in children and adolescents whose parents and guardians are involved in the care of the patients. Family support and involvement of parents/guardians is an important modifiable factor and has been found to promote adherence and optimal glycaemic control in a study by Anderson *et al.*[206]. In addition, a recent meta-analysis by Tsiouli *et al.*[209] demonstrated that family conflict was associated

with poor glycaemic control. This present study found a significant association between caregiver involvement in the diabetes-related tasks of insulin injection and BGM and good glycaemic control. This can be explained by the fact that, in the setting where this study was carried out, parents will continuously offer psychosocial support and assume the responsibility of care to all sick children regardless of age and degree of maturity by providing an appropriate diet and administration of medication. Also, this indicates the importance of the parent-child relationship in effective diabetes management because it is believed that the way in which the family deals with the disease has an impact on how the glycaemic control evolves.

Similar findings have been reported in other studies[207,208]. In addition, a study by Berg *et al.*[243] on parental involvement in the diabetes management of adolescents with type 1 diabetes found a direct association between parent-adolescent relationship and monitoring with better adherence and glycaemic control. However, research by Lewin *et al.*[244] and Sweenie *et al.*[245] have demonstrated poor adherence resulting in poor glycaemic control among children of all ages with critical parent-child relationships. Further, Anderson *et al.*[246] in a study to identify aspects of family behaviour associated with glycaemic control among youths (9 to 14 years) found that family conflict was significantly associated with poor glycaemic control during this transition period to adolescence.

The multivariate analysis in this study confirmed that minimal/moderate caregiver involvement in the task of insulin injection was a significant independent predictor of poor glycaemic control.

However, it is a well-known fact that family dynamics, stages of development, and physiological changes resulting from sexual maturity are important in the development and implementation of an optimal diabetes regimen in adolescents and there is need for a balance between adult supervision and self-care as the child reaches maturity. This finding has potential clinical implications for intervention as emphasis on optimal caregiver involvement in diabetes related tasks of children targeting parents and caregivers could be addressed through planned educational programs and this will ultimately improve type 1 diabetes management and optimize HbA1c in the study setting.

Adherence to the different treatment aspects represents an important factor in determining good glycaemic control and eventually better treatment outcome. Effective treatment of diabetes requires patient adherence to a complex care regimen which encompasses multiple insulin administration, frequent BGM and careful monitoring of diet and physical activity. This poses a significant burden to children with type 1 diabetes and their families. Moreover, adherence to these multiple diabetes tasks is very challenging to diabetic patients of all ages especially adolescents who are grappling with rapid biological and hormonal changes due to puberty, which tend to antagonize the action of insulin as well as independence from parents to increased responsibility for their T1D management.

In this study, a significant association was observed between good adherence to BGM and good adherence to insulin injection and good glycaemic control. However, no such association was observed with diet. Some of the reasons given for poor adherence to insulin injection included forgetfulness, lack of food and the fact that it was not convenient injecting insulin in school and other public places. Also, the most common reason cited for non-adherence to BGM was laziness. Similar findings have been reported by Borus and Laffel[118]. Several studies have examined the relationship between glycaemic control and adherence including Hood *et al.*[121] in a meta-analysis which demonstrated a negative correlation between treatment adherence and HbA1c levels in children and adolescents with type 1 diabetes. Nonetheless, this was found to be independent of sociodemographic and other diabetes specific variables. This points to the fact that glycaemic control improves with improved adherence in children and adolescents irrespective of sociodemographic and diabetes-specific characteristics.

Mehta *et al.*[213] demonstrated that greater dietary adherence was associated with lower HbA1c levels in young patients with diabetes, a finding that was not confirmed in this study. However, the 24 hour recall method of dietary analysis used in this study may not represent the habitual nutrient intake.

The lack of association between HbA1c and adherence to diet might be explained by the fact that assessment of adherence to the different treatment regimens was by self–reporting.

Recall bias could have been possible and over reporting could have resulted in falsely elevated adherence levels. Also, adherence to diet was assessed using the 24 hours prior to the study, while patient adherence to BGM and insulin was done for the week before the study visit and this might not be a true reflection of the patients' overall adherence in the whole country.

This section had some limitations which are worth mentioning. The cross-sectional nature of this study cannot show elements of causality. Also, the interpretation of caregiver involvement in diabetes related tasks is limited by the fact that the caregiver adjustment was not analyzed in an age-adjusted mode. It was also difficult finding validated tools for insulin, dietary and blood glucose monitoring adherence that could be applicable in the study setting. BGM adherence can be assessed by downloading data from the blood glucose monitors, while dietary adherence can be assessed by counting the calories in the diet. This was not performed in our study but should be considered in future trials.

4.3. Diabetic ketoacidosis (DKA) and glycaemic control.

Diabetic ketoacidosis remains the most common cause of hospitalization and mortality among children with type 1 diabetes. Also, children and adolescents with ketoacidosis usually have higher levels of HbA1c. The clinical pattern includes polyuria and polydipsia as well as fatigue, coma and weight loss as the most commonly reported symptoms at diagnosis.

This present study found that less than 30% of children and adolescents presented with DKA at diagnosis and this group of patients had a higher mean HbA1c compared to those who did not present with ketoacidosis. Nevertheless, there was no significant difference in the glycaemic control among the two groups. Also, children/adolescents presenting with DKA had elevated plasma glucose levels compared to the non-DKA group. Compared to reports from other African countries such as Nigeria[247] and Tanzania[126], this observed prevalence is low. It is difficult making comparisons with other studies given the wide scope of definitions used for diabetic ketoacidosis.

Similar findings have been reported in other studies[148,149,248]. For instance, in a study by Onyiriuka and Ifebi[247] in Nigeria, it was reported that 77.1% of children and adolescents presented with DKA at onset of type 1 diabetes. On the contrary, Fritsch *et al.*[249] in a multicenter study to determine the incidence and risk factors for DKA among 28,770 type 1 diabetic children/adolescents < 20 years, from Germany and Austria reported that less than 5% of the patients presented with one episode of DKA with a significantly higher rate reported in females and in children of migrants.

The frequency of DKA at diagnosis observed in this study was relatively low and this could be as a result of the fact that children experiencing severe DKA are not diagnosed correctly and may die before the correct diagnosis is made.

The limitation of this section is that clinical evidence for DKA at diagnosis was assessed by the presence or absence of certain symptoms or complaints reported by the patient and/or caregiver; as such findings on diabetic ketoacidosis should be interpreted with caution. Moreover, ketoacidosis is usually defined as blood pH of less than 7.3[250], with the severity of acidosis categorized into mild, blood pH 7.2 – 7.3; moderate, blood pH 7.1 – < 7.2; and severe, blood pH < 7.1. Even so, this was not carried out in our study population. Urinalysis was not done for all the patients at diagnosis as such the results cannot be generalized for the study population.

4.4. The impact of type 1 diabetes on the daily life of patients.

The transition to adolescence among youths with type 1 diabetes has been found to be associated with unique challenges especially for girls resulting in deteriorating glycaemic control, poor adherence to treatment and increased risk of psychological disorders[251]. In a review by Jack[252] these challenges were classified into biological influences such as physical and emotional changes during puberty, psychological and behavioural factors such as stress and sociocultural factors like peer pressure. Hassan *et al.*[253] in a study examining the association between psychosocial factors and glycaemic control among children with type 1

diabetes aged 8 to 17 years found that 9.5% of the poorly controlled subjects had depression compared to 3% of children with good glycaemic control. The authors also found that the quality of life also deteriorated with poor glycaemic control. Also, a study by Hapunda *et al.*[254] among adolescents living with type 1 diabetes in Zambia to identify the sources of stress as well as the perceived quality of life and care experienced by these adolescents found physical, social and psychological factors as the most common sources of stress, while quality of healthcare was affected mostly by lack of drugs, lack of proper nutrition and low socioeconomic status.

In this study, it was found that more than 70% of the children reported that diabetes had a negative impact on their daily life. Nonetheless, there was no significant difference in mean HbA1c among children who reported a negative impact on their life and those on whom diabetes had no impact. Given the fact that the perception of the caregiver or children was the method used in evaluating the impact of T1D on daily life, it might have contributed to the lack of significance in glycaemic control among the two groups. Moreover, an objective assessment of type 1 diabetes impact and quality of life of the children were beyond the scope of this study.

4.5. Methodological considerations.

The data used in this current study was obtained from only one region (North West) out of the 10 administrative regions in the country. As such findings might not be a true reflection of the situation of children living with type 1 diabetes in the country. Moreover, the cross-sectional nature of this study only allows for the examination of associations but cannot show elements of causality. Data from all the 10 regions of the country is necessary for effective interventions because the different regions have different cultures and this cultural diversity affects patient treatment preferences and health seeking behaviour. Hill[255] in a study had proposed certain criteria that can be used to examine causality, which are often used in epidemiological studies. However, there is no consensus as to whether these variables could be applicable in all settings.

Also, given the distribution of HbA1c values observed in the study cohort, a compromise was made on the HbA1c level used to define "good" glycaemic control. Although the current recommendation from the ADA[107] state that good glycaemic control is HbA1c < 7.5%, these goals are very difficult to achieve even in clinical trial settings. Thus, it was demonstrated in the Diabetes Control and complications trial that even in the intensive group, the HbA1c level achieved was > 1% higher than the current ADA recommendations for the patients in general and in adolescence it was worse partly because this is a period of rapid biological changes and they are trying to gain independence from their parents. Studies in developed countries[120,125,191] have shown that mean HbA1c levels are generally > 8.0% despite advances in insulin therapeutics that ease insulin delivery. In addition, adherence to the different diabetes regimens is still problematic to children in all age groups especially adolescence. A target HbA1c of < 9.0% was set for this study, a value slightly above the mean HbA1c levels attained in the developed nations due to the poor glycaemic control reported in most African studies[126,128,236]. Also, the lack of resources and knowledge deficit among patients and their families on the need for optimizing glycaemic control in the study setting contributed to the setting of a 1.5% higher HbA1c level target above the recommendations of the ADA.

In addition, the tools used in this study for the measurement of adherence are those used in the various clinics to review the children/adolescents because it was not possible to find validated tools for insulin, dietary and blood glucose monitoring adherence that could be relevant in the study setting. Further, adherence to diet was assessed using the 24 hour dietary recall by Geissler and Powers[233], adherence to blood glucose monitoring according to Hood *et al.*[121] and adherence to insulin according to the Diabetes Control and complications trial[116] (intensive insulin treatment).

Finally, the findings of this study are only applicable to children/adolescents attending the outpatient clinics for children living with type 1 diabetes in Cameroon. Whether or not the findings also hold true in other settings cannot be deduced from this study.

Despite the limitations of this study, it is strengthened by the fact that it has provided for the first time data on predictors of good and poor glucose control among children/adolescents with type 1 diabetes in the North West Region of Cameroon. It has also demonstrated the importance of a mother in the management of paediatric type 1 diabetes care. In addition, it has shown that the active involvement of the caregiver in the task of insulin injection optimizes glycaemic control in children and adolescents with type 1 diabetes. The factors identified in this study which are significantly associated to glycaemic control are modifiable. These findings can contribute in improving the registry's intervention program that is already going on to better address the needs of the children.

4.6. Conclusions and implications.

This study among type 1 diabetic children in the North West Region of Cameroon shows that the mother's involvement in the diabetes management of their children is a very important determinant for good glucose control. The mother as a primary caregiver may just be an indicator and not a causal factor for better glucose control. Thus, it may reflect a setting related to (but not restricted to) family dynamics, stages of development and physiological differences resulting from sexual maturity allowing better glucose control.

The main findings of this study are summarized as follows:

- Despite the free and regular supply of insulin and blood glucose monitors through Changing Diabetes in Children (CDiC) program, glycaemic control among children and adolescents with type 1 diabetes attending the clinics for children living with diabetes in the North West Region of Cameroon remains very poor. However, there was a significant decrease in HbA1c from diagnosis to the study period.
- Being on twice daily insulin injections was associated with better glycaemic control.
- Younger age, shorter diabetes duration and family living arrangements did not influence glycaemic control.
- There was a significant association between adherence to insulin injection and adherence to BGM with glycaemic control. However, there was no significant association between diet and HbA1c.

- More visits to the diabetic clinic were found to be significantly associated with good glyceamic control.
- Having a mother as the primary caregiver and minimal/moderate caregiver involvement in the task of insulin injection were significant independent predictors of good and poor glycaemic control respectively.
- Type 1 diabetes was found to have an impact on the daily life of patients.

The study findings have potential implications for effective interventions in the delivery of care for children/adolescents with type 1 diabetes, prevention and for future studies.

This study has demonstrated that glycaemic control is still poor among children and adolescents in the North West Region irrespective of the fact that the intervention through CDiC provides free insulin and blood glucose monitors. Most interventions on type 1 diabetes in children have been carried out in developed countries. The Changing Diabetes in Children program is the first intervention in Cameroon for children living with type 1 diabetes. Even though the program appears to be working, the mean glycaemic control among the children remains poor with values above the recommended ADA target of < 7.5% as well as the set target in this study (HbA1c < 9.0%). It is important to note that although most of the children have poor glycaemic control, they could have been much worse if they were not included in the program at all.

The implications for the above are that since the management of diabetes requires a complex treatment approach, any intervention should therefore focus on the aspects of behaviour (individual level), and culture (population level) which could play a vital role in understanding why most of the children and adolescents in our setting had high levels of HbA1c. Also, metabolic control is only one of the approaches of maintaining good glucose control as such focusing on biochemical parameters alone is unlikely to prevent deterioration in glycaemic control in this setting. In addition, individual and population level factors may contribute in understanding why younger age and shorter diabetes duration were not significantly associated with glycaemic control in our study. In actual fact, a study in

Sudan among type 1 diabetics also found that younger age was not significantly associated with good glycaemic control[128].

Also, given the complexity involved in the management of diabetes, diversity of cultures as well as the individual/family preferences in the different ethnic groups in the country that could affect treatment decisions for patients, healthcare providers need to make use of strategies like the trans-cultural patient care[256,257]. This approach would not only build confidence in patients, it could promote the use of culture among health professionals[258]. This can lead to better adherence to treatment especially among adolescents as well as inspire the health professionals to follow up this group of patients. It is worth noting that Cameroon has 10 regions with different cultures. There is therefore need to start identifying individual and cultural factors in the different regions that could affect treatment decisions for patients and this will help in reducing the rates of poor glycaemic control among type 1 diabetic children. Also, these factors could be crucial in understanding why family living arrangement was not significantly associated with glucose control in this study. In addition, these cultural factors could help the responsible persons of the registry to better address the needs of these diabetic children given the fact that some cultural factors that could improve the management of the disease in one region might not be applicably or effective in other regions.

Late diagnosis is as a result of ignorance and lack of knowledge. Therefore from an epidemiological point of view, public awareness (through educational programs) needs to be created especially focusing on healthcare professionals, parents, and caregivers to sensitize them on the early signs of diabetes because only a higher level of public awareness can prevent missed and delayed diagnosis and improve metabolic control in this paediatric population. Nonetheless, a study in India found a significant improvement in the knowledge and attitude but no improvement in HbA1c levels after a planned educational intervention program on the attitudes, knowledge, and practices of type 1 diabetics[221].

Our study demonstrated that having a mother as a primary caregiver and that minimal/moderate caregiver involvement in the task of insulin injection were significantly

associated with good and poor glucose control as measured by HbA1c respectively. This indicates that effective educational intervention addressing knowledge deficiencies should begin at the level of the family (especially parents/and caregivers) and then the rest of the family as more educational sessions on the importance of optimal involvement in the diabetes care of children will increase their knowledge of the disease management and ultimately improved glucose control among the children.

Socioeconomic status was not significantly associated with glycaemic control in this study. Most epidemiological studies often use educational level, income and occupation as indicators of SES and there is a possibility that these variables could be inter-related. Since this study involved children and adolescents (who depend mostly on their parents because they might be unable to earn a living on their own), their SES could only be determined using that of their parents. In the present study it was the Cameroon public service classification of civil servants of income and occupation. There is no best way of estimating SES since the different indicators could represent different concepts of SES[259]. A previous study by Fezeu *et al.*[260] indicated that in Cameroon, educational level seems not to be a good indicator for SES as being educated is not usually associated with a good income. Our study made use of occupation and income in order to demonstrate their contribution and impact on health inequalities with respect to type 1 diabetes in children. The implications of the above is therefore that any intervention to improve on type 1 diabetes management and outcome in children should target the rural areas in particular and then extend to the urban areas of the country since this study has found that a majority of the study participants were from the rural area and of low SES.

From a dietary perspective, there was no significant association between adherence to diet and glycaemic control. Also, there is variation in the staple foods consumed by the different ethnic groups in the different regions of the country. The implications of the above finding is that dietary adherence will continue to be poor if something is not done to enable the children to be able to quantify the calories in their diet given the fact that there is no food composition data that could be of help in quantifying the nutrient intake of the children. There is therefore need to make an assessment of the nutrients and calories found in the

staple foods frequently consumed by the different ethnic groups. The use of nutrient composition data to assess foods consumed by these children could contribute in understanding why only a tenth of the study participants had good dietary adherence.

Further research should be carried out in children in other type 1 diabetic clinics in the other regions of the country because the findings may slightly differ between regions due to the cultural diversity in the country. Finally, there is a need to start etiological and prevention research in the country and this should target behavioural, biological and the environmental factors that could help in implementing effective strategies to prevent deterioration in type 1 diabetes control in the country and rural sub-Saharan Africa.

5. SUMMARY

Like the rest of the world, some families in sub-Saharan Africa (SSA) are also affected with type 1 diabetes. In contrast to Western countries, type 1 diabetes is associated with a very poor prognosis in sub-Saharan Africa with many patients not being diagnosed and those diagnosed having a life expectancy of less than a year. In developed countries, a variety of factors that predict the outcome of children with type 1 diabetes has been documented while there is limited information on predictors of outcome in sub-Saharan Africa.

In Cameroon, the "Changing Diabetes in Children" (CDiC) program is an intervention, which helps to increase access to care for children suffering from type 1 diabetes and the key components of the program include therapy supplies, education and training of healthcare professionals for early diagnosis and adequate management of type 1 diabetes. This study identifies that mother as a primary caregiver and the involvement of the caregiver in diabetes related task can help in improving glucose control in children and adolescents with type 1 diabetes in the North West Region of Cameroon.

These findings are to help members of the registry to improve on the current intervention in the country.

Chapter 1 of this thesis exploits the different forms of diabetes leading to the description of type 1 diabetes as well as the genetics, immune markers and the environmental risk factors involved in the pathogenesis of the disease. It then exploits the literature on the global

situation looking at the incidence and prevalence of type 1 diabetes from a global perspective leading to the situation in Cameroon. The different diabetes complications which depend on glucose control, potential predictors of glycaemic control and the challenges in diabetes management are presented.

The method used in the study, the study participants, study site and the management of patients is presented in chapter 2. This study included 76 children and adolescents with type 1 diabetes in the North West region of Cameroon. Also, a convenience sampling technique was used because the patients were involved in a national program that is already running in hospital clinics in the country and data was collected from all the children that were included in the program who consented to the study. The study investigated predictors of good and poor glycaemic control using information on diabetes-related characteristics and practices, clinical and biochemical parameters as well as sociodemographic characteristics.

Chapter 3 presents the main characteristics of the study population, the differences in clinical and biochemical characteristics before diagnosis and during the study period and the mean HbA1c by diabetes specific characteristics. The findings show that children whose mothers are the primary caregivers have better glycaemic control compared to those having someone other than the mother as a primary caregiver. This is then followed by the association between caregiver involvement in diabetes–related activities and patient adherence which indicate that optimal caregiver involvement in diabetes related activities translate to better glycaemic control. Binary logistic regression analysis to identify potential determinants of poor glycaemic control followed by multivariate analysis demonstrate that children with minimal/moderate caregiver involvement in the task of insulin injection are at risk of poor glycaemic control as measured by HbA1c. Further, it was confirmed from the multivariate analysis that having a mother as a primary caregiver is an important predictor of good glycaemic control in the children.

This study has shown that glycaemic control among children and adolescents in the study setting is very poor despite the free and regular supply of insulin and free glucose monitors.

This point to the fact that there is still a huge knowledge gap between the standards of medical care and practice as well as some underlying individual and population level determinants causing poor control in the children/adolescents included in the CDiC program which need to be identified to help members of the diabetes registry to modify the current intervention or design future interventions

6. REFERENCES

1. American Diabetes Association, 2014, 'Diagnosis and classification of diabetes mellitus', *Diabetes Care*, **37,** Suppl 1, S81- S90.

2. Anderson, MS, Bluestone, JA, 2005, 'The NOD mouse: a model of immune dysregulation', *Annu. Rev. Immunol*, **23**, 447–485.

3. Hall, V, Thomsen, RW, Henriksen, O, Lohse, N, 2011, 'Diabetes in Sub Saharan Africa 1999-2011: Epidemiology and public health implications, a systematic review', *BMC Public Health*, **11**(564), 1-12.

4. American Diabetes Association, 1997, 'Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus', *Diabetes Care*, **20**(7), 1183-1197.

5. Pinhas-Hamiel, O, Zeitler, P, 2005, 'The global spread of type 2 diabetes mellitus in children and adolescents', *J Pediatr*, **146**, 693–700.

6. Neu, A, Feldhahn, L, Ehehalt, S, Hub, R, Ranke, MB; DIARY group Baden-Württemberg, 2009, 'Type 2 diabetes mellitus in children and adolescents is still a rare disease in Germany: a population-based assessment of the prevalence of type 2 diabetes and MODY in patients aged 0-20 years', *Pediatr Diabetes*, **10**(7), 468-473.

7. Reinehr, T, 2013, 'Type 2 diabetes mellitus in children and adolescents', *World J Diabetes*, **4**(6), 270-281.

8. Haines, L, Wan, KN, Lynn, R, Barrett, TG, Shield, JPH, 2007, 'Rising incidence of type 2 diabetes in children in the UK', *Diabetes Care*, **30**(5), 1097-1101.

9. Atkinson, MA, 2012, 'The pathogenesis and natural history of type 1 diabetes', *Cold Spring Harb Perspect*, **2**, a007641.

10. Bluestone, JA, Herold, K, Eisenbarth, G, 2010, 'Genetics, pathogenesis and clinical interventions in type 1 diabetes', *Nature*, **464**, 1293- 1300.

11. Haller, MJ, Atkinson, MA, Schatz, D, 2005, 'Type 1 diabetes mellitus: etiology, presentation and management', *Pediatr Clin N Am*, **52**, 1553– 1578.

12. American Diabetes Association, 2010, 'Diagnosis and classification of diabetes mellitus', *Diabetes Care*, **33,** Suppl 1, S62-69.

13. Padoa, C, 2011, 'The epidemiology and pathogenesis of type 1 diabetes mellitus in Africa', *JEMDSA*, **16**(3), 130-136.

14. International Diabetes Federation, 2015, *IDF Diabetes Atlas, 7th Edition*, Brussels, Belgium: International Diabetes Federation, Retrieved on January 13, 2016, from http://www.diabetesatlas.org

15. American Diabetes Association, 2008, 'Diagnosis and classification of diabetes mellitus', *Diabetes Care*, **31,** Suppl 1, S55-60.

16. Leslie, RDG, Kolb, H, Schloot, NC, Buzzetti, R, Mauricio, D, De Leiva, A, Yderstraede, K, Sarti, C, Thivolet, C, Hadden, D, Hunter, S, Schernthaner, G, Scherbaum, W. Williams, R, Pozzilli, P, 2008, 'Diabetes classification: grey zones, sound and smoke: Action LADA 1', *Diabetes Metab Res Rev*, **24**(7), 511-9.

17. Kyvik, KO, Nystrom, L, Gorus, F, Songini, M, Oestman, J, Castell, C, Green, A, Gyurus, E, Ionescu-Tirgoviste, C, Mckinney, PA, Michalkova, D, Ostrauskas, R, Raymond, NT, 2004, 'The epidemiology of Type 1 diabetes mellitus is not the same in young adults as in children', *Diabetologia*, **47**(3), 377-84.

18. Sosenko, JM, Skyler, JS, Krischer, JP, Greenbaum, CJ, Mahon, J, Rafkin, LE, Cuthbertson, D, Cowie, C, Herold, K, Eisenbarth, G, Palmer, JP, Diabetes Prevention Trial-Type 1 Study Group, 2010, 'Glucose excursions between states of glycemia with progression to type 1 diabetes in the diabetes prevention trial-type 1 (DPT-1)', *Diabetes*, **59**(10), 2386–2389.

19. Baekkeskov, S, Aanstoot, HJ, Christgau, S, Reetz, A, Solimena, M, Cascalho, M, Folli, F, Richter-Olesen, H, De Camilli, P, 1990, 'Identification of the 64K autoantigen in insulin-dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase', *Nature*, **347**(6289), 151-6.

20. Lan, MS, Wasserfall, C, Maclaren, NK, Notkins, AL, 1996, 'IA-2, a transmembrane protein of the protein tyrosine phosphatase family, is a major autoantigen in insulin-dependent diabetes mellitus', *Proc Natl Acad Sci U S A*, **93**(13), 6367-6370.

21. Wenzlau, JM, Juhl, K, Yu, L, Moua, O, Sarkar, SA, Gottlieb, P, Rewers, M, Eisenbarth, GS, Jensen, J, Davidson, HW, Hutton, JC, 2007, 'The cation efflux transporter ZnT8 (Slc30A8) is a major autoantigen in human type 1 diabetes', *Proc Natl Acad Sci U S A*, **104**(43), 17040-17045.

22. von Herrath, M, Sanda, S, Herold, K, 2007, 'Type 1 diabetes as a relapsing-remitting disease?', *Nat Rev Immunol*, **7**(12), 988-94.

23. Hawa, MI, Picardi, A, Costanza, F, D'Avola, D, Beretta Anguissola, G, Guglielmi, C, Mottini, G, Fezeu, L, Mbanya, JC, Leslie, RD, Pozzilli, P, 2006, 'Frequency of diabetes and thyroid autoantibodies in patients with autoimmune endocrine disease from Cameroon', *Clin Immunol*., **118**(2-3), 229-232.

24. Lutale, J, Thordarson, H, Holm, P, Eide, G, Vetvik, K, 2007, 'Islet cell autoantibodies in African patients with Type 1 and Type 2 diabetes in Dar es Salaam Tanzania: a cross sectional study', *J Autoimmune Dis*, **4**(4), 1-7.

25. Fakhfakh, R, Haddouk, S, Hadj Hamida, YB, Kamoun, T, Ayed, MB, Hachicha, M, Masmoudi, H, 2008, 'Pancreatic autoantibodies in Tunisian children with newly diagnosed type 1 diabetes', *Pathol Biol (Paris)*, **56**(3), 130-2.

26. Noble, JA, Erlich, HA, 2012, 'Genetics of type 1 diabetes', *Cold Spring Harb Perspect Med*, **2**, a007732.

27. Redondo, MJ, Fain, PR, Eisenbarth, GS, 2001, 'Genetics of type 1A diabetes', *Recent Prog Horm Res***, 56**, 69–89.

28. Redondo, MJ, Jeffrey, J, Fain, PR, Eisenbarth, GS, Orban, T, 2008, 'Concordance for islet autoimmunity among monozygotic twins', *N Engl J Med*, **359**, 2849–2850.

29. Akerblom, HK, Vaarala, O, Hyoty, H, Ilonen, J, Knip, M, 2002, 'Environmental factors in the etiology of type 1 diabetes', *Am J Med Genet*, **115**(1), 18–29.

30. Knip, M, Simell, O, 2012, 'Environmental Triggers of Type 1 Diabetes', *Cold Spring Harb Perspect Med*, **2:**a007690.

31. Metcalfe, KA, Hitman, GA, Rowe, RE, Hawa, M, Huang, X, Stewart, T, Leslie, RDG, 2001, 'Concordance for Type 1 Diabetes in Identical Twins Is Affected by Insulin Genotype', *Diabetes Care*, **24**(5), 838-842.

32. Kaprio, J, Tuomilehto, J, Koskenvuo, M, Romanov, K, Reunanen, A, Eriksson, J, Stengård, J, Kesäniemi, YA, 2001, 'Concordance for type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in a population-based cohort of twins in Finland', *Diabetologia*, **35**(11), 1060-7.

33. Mehers, KL, Gillespie, KM, 2008, 'The genetic basis for type 1 diabetes', *Brit Med Bull*, **88**(1), 115-129.

34. Virtanen, SM, Knip, M, 2003, 'Nutritional risk predictors of beta cell autoimmunity and type 1 diabetes at a young age', *Am J Clin Nutrit*, **78**(6), 1053-1067.

35. Gale, EA, 2002, 'The rise of childhood type 1 diabetes in the 20th century', *Diabetes,* **51**(12), 3353-3361.

36. EURODIAB ACE Study Group, 2000, 'Variation and trends in incidence of childhood diabetes in Europe', *Lancet*, **355**(9207), 873-6.

37. Akerblom, HK, Knip, M, 1998, 'Putative environmental factors in Type 1 diabetes', *Diabetes Metab Rev*, **14**(1), 31-67.

38. Rewers, M, Norris, J, Dabelea, D, 2004, 'Epidemiology of type 1 diabetes mellitus', *Adv Exp Med Biol*, **552**, 219-246.

39. Maahs, DM, West, NA, Lawrence, JM, Mayer-Davis, EJ, 2010, 'Chapter 1: Epidemiology of Type 1 Diabetes', *Endocrinol Metab Clin North Am*, **39**(3), 481–497.

40. Richer, MJ, Horwitz, MS, 2009, 'Coxsackievirus infection as an environmental factor in the etiology of type 1 diabetes', *Autoimmun Rev*, **8**(7), 611-5.

41. Visalli, N, Sebastiani, L, Adorisio, E, Conte, A, De Cicco, AL, D'Elia, R, Manfrini, S, Pozzilli, P, IMDIAB Group, 2003, 'Environmental risk factors for type 1 diabetes in Rome and province', *Arch Dis Child***, 88**(8), 695-698.

42. Cardwell, CR, Carson, DJ, Patterson, CC, 2005, 'Parental age at delivery, birth order, birth weight and gestational age are associated with the risk of childhood Type 1 diabetes: a UK regional retrospective cohort study', *Diabet Med*, **22**(2), 200-6.

43. Cardwell, CR, Stene, LC, Joner, G, Bulsara, MK, Cinek, O, Rosenbauer, J, Ludvigsson, J, Jané, M, Svensson, J, Goldacre, MJ, Waldhoer, T, Jarosz-Chobot, P, Gimeno, SGA, Chuang, L-M, Parslow, RC, Wadsworth, EJK, Chetwynd, A, Pozzilli, P, Brigis, G, Urbonaitė, B, Šipetić, S, Schober, E, Devoti, G, Ionescu-Tirgoviste, C, de Beaufort, CE, Stoyanov, D, Buschard, K, Patterson CC, 2010, 'Maternal Age at Birth and Childhood Type 1 Diabetes: A Pooled Analysis of 30 Observational Studies', *Diabetes,* **50**, 486–494.

44. Lammi, N, Moltchanova, E, Blomstedt, PA, Tuomilehto, J, Eriksson, JG, Karvonen, M, 2009, 'Childhood BMI trajectories and the risk of developing young adult-onset diabetes', *Diabetologia*, **52**(3):408-14.

45. Harder, T, Roepke, K, Diller, N, Stechling, Y, Dudenhausen, JW, Plagemann, A, 2009, 'Birth weight, early weight gain, and subsequent risk of type 1 diabetes: systematic review and meta-analysis', *Am J Epidemiol*, **169**(12), 1428-36.

46. Dong, J-Y, Zhang, W, Chen, JJ, Zhang, Z-L, Han, S-F, Qin, L-Q, 2013, 'Vitamin D Intake and Risk of Type 1 Diabetes: A Meta-Analysis of Observational Studies', *Nutrients***, 5**, 3551-3562.

47. Zipitis, CS, Akobeng, AK, 2008, 'Vitamin D Supplementation in Early Childhood and Risk of Type 1 Diabetes: a Systematic Review and Meta-analysis', *Arch. Dis. Child*, doi:10.1136/adc.2007.128579.

48. Knip, M, Virtanen, SM, Akerblom, HK, 2010, 'Infant feeding and the risk of type 1 diabetes', *Am J Clin Nutr*, **91**(suppl), 1506S–13S.

49. Cardwell, CR, Stene, LC, Joner, G, Cinek, O, Svensson, J, Goldacre, MJ, Parslow, RC, Pozzilli, P, Brigis, G, Stoyanov, D, Urbonaité, B, Šipetić, S, Schober, E, Ionescu-Tirgoviste, C, Devoti, G, de Beaufort, CE, Buschard, K, Patterson CC, 2008, 'Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies', *Diabetologia*, **5**1(5), 726-735.

50. Leslie, RD, Castelli, MD, 2004, 'Perspectives in diabetes: Age dependent influences on the origins of autoimmune diabetes', *Am Diab Ass*, **53**(12), 3033-3040.

51. Majeed, AAS, Hassan, MK, 2011, 'Risk Factors for Type 1 Diabetes Mellitus among children and adolescents in Basrah', *Oman Medical Journal*, **26**(3), 189-195.

52. Mattsson, K, Jönsson, I, Malmqvist, E, Larsson, HE, Rylander, L, 2015, 'Maternal smoking during pregnancy and offspring type 1 diabetes mellitus risk: accounting for HLA haplotype', *Eur J Epidemiol*, DOI10.1007/s10654-014-9985-1.

53. Bingley, PJ, Douek, IF, Rogers, CA, Gale, EA, 2000, 'Influence of maternal age at delivery and birth order on risk of type 1 diabetes in childhood: prospective population based family study. Bart's-Oxford Family Study Group', *BMJ*, **321**(7258), 420-424.

54. D'Angeli, MA, Merzon, E, Valbuena, LF, Tirschwell, D, Paris, CA, Mueller, BA, 2010, 'Environmental factors associated with childhood-onset type 1 diabetes mellitus: an exploration of the hygiene and overload hypotheses', *Arch Pediatr Adolesc Med*, **164**(8),732-738.

55. Stene, LC, Magnus, P, Lie, RT, Søvik, O, Joner, G, the Norwegian Childhood Diabetes Study Group, 2001, 'Maternal and paternal age at delivery, birth order, and risk of childhood onset type 1 diabetes: population based cohort study', *BMJ,* **323**, 1–4.

56. Ievins R, Roberts, SE, Goldacre, MJ, 2007, 'Perinatal factors associated with subsequent diabetes mellitus in the child: record linkage study', *Diabet Med*, **24**(6), 664-670.

57. Stuebe, A, 2009, 'The risks of not breastfeeding for mothers and infants', *Rev Obstet Gynecol,* **2**(4), 222-231.

58. Stene, LC, Magnus, P, Lie, RT, Søvik, O, Joner, G, the Norwegian Childhood Diabetes Study Group, 2001, 'Birth weight and childhood onset type 1 diabetes: population based cohort study, *BMJ*, **322**, 889-892.

59. Karamizadeh, Z, Jalaeian, H, Kashef, MA, Ebrahimi, M, 2006, 'Birth Weight and Childhood Onset Type 1 Diabetes: A Case-Control Study in Shiraz, South of Iran', *Iran J Med Sci*, **31**(3), 164-166.

60. Harder, T, Roepke, K, Diller, N, Stechling, Y, Dudenhausen, JW, Plagemann, A, 2009, 'Birth weight, early weight gain, and subsequent risk of type 1 diabetes: systematic review and meta-analysis', *Am J Epidemiol,* **169**(12), 1428-1436.

61. Dabelea, D, Rewers, A, Stafford, JM, Standiford, DA, Lawrence, JM, Saydah, S, Imperatore, G, D'Agostino Jr, RB, Mayer-Davis, E, Catherine Pihoker, C, 2014, 'Trends in the Prevalence of Ketoacidosis at Diabetes Diagnosis: The SEARCH for Diabetes in Youth Study', *Pediatrics*, **133**, e938–e945.

62. Eliasson, M, Brostrom, G, 2006, 'Major public health problems – diabetes', *Scandinavian Journal of Public Health*, **34**(Suppl 67), 59–68.

63. Hall, V, Thomsen, RW, Henriksen, O, Lohse N, 2011, 'Diabetes in Sub Saharan Africa 1999-2011: Epidemiology and public health implications, a systematic review' *BMC Public Health*, **11**(564), 1-12.

64. La Roche, 2011, Corporate responsibility, Changing Diabetes in Children, La Roche, Switzerland, Hoffman, F,- La Roche Ltd, Retrieved on March 13, 2015, from www.roche.com/diabetes_in_children.

65. Levitt, NS, 2008, 'Diabetes in Africa: epidemiology, management and healthcare challenges', *Heart*, **94**(11), 1376-82.

66. Mbanya, JCN, Motala, AA, Sobngwi, E, Assah, FK, Enoru, ST, 2010, 'Diabetes in sub-Saharan Africa', *Lancet*, **375**, 2254–66.

67. International Insulin Foundation RAPIA Initiative, Retrieved on January 17, 2016, from https://www.idf.org/webdata/docs/IIF-RAPIA_plan.

68. DIAMOND Project Group, 2006, 'Incidence and trends of childhood type 1 diabetes worldwide 1990-1999', *Diabet Med*, **23** (8), 857-866.

69. Patterson, CC, Dahlquist, GG, Gyürüs, E, Green, A, Soltesz, G, EURODIAB study Group, 2009, 'Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study', *Lancet*, **373** (9680), 2027-2033.

70. Liese, AD, D'Agostino, RB, Hamman, RF, Kilgo, PD, Lawrence, JM, Liu, LL, Loots, B, Linder, B, Marcovina, S, Rodriguez, B, Standiford, D, Williams, DE, SEARCH for Diabetes in Youth Study Group, 2006, 'The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study', *Pediatrics*, **118** (4), 1510-1518.

71. Diabetes Epidemiology Research International Group, 1988, 'Geographic patterns of childhood insulin-dependent diabetes mellitus', *Diabetes*, **37**(8), 1113-1119.

72. Karvonen, M, Viik-Kajander, M, Moltchanova, E, Libman, I, LaPorte, R, Tuomilehto, J, 2000, 'Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group', *Diabetes Care*, **23**(10), 1516-1526.

73. Pettitt, DJ, Talton, J, Dabelea, D, Divers, J, Imperatore, G, Lawrence, JM, Liese, AD, Linder, B, Mayer-Davis, EJ, Pihoker, C, Saydah, SH, Standiford, DA, Hamman, RF, for the SEARCH for Diabetes in Youth Study Group, 2014, 'Prevalence of diabetes in U.S. youth in 2009: The SEARCH for Diabetes in Youth Study', *Diabetes Care*, **37**(2), 402-408.

74. Maahs, DM, West, NA, Lawrence, JM, Mayer-Davis, EJ, 2010, 'Chapter 1: Epidemiology of Type 1 Diabetes', *Endocrinol Metab Clin North Am*, **39**(3), 481–497.

75. Soltesz, G, 2009, 'Worldwide childhood type 1 diabetes epidemiology', *Endocrinol Nutr,* **56** (Supl 4), 53-55.

76. Kumar, P, Krishna, P, Reddy, SC, Gurappa, M, Aravind, SR, Munichoodappa C, 2008, 'Incidence of type 1 diabetes mellitus and associated complications among children and young adults: results from Karnataka Diabetes Registry 1995-2008', *J Indian Med Assoc*, **106**(11), 708-11.

77. Peers, N, Kengne. AP, Motala, AA, Mbanya, JC, 2013, 'Diabetes in the African region: an update', *Diabetes Research in Clinical Practice*, **103**(2014), 197-205.

78. Bessaoud, K, Boudraa, G, Deschamps, I, Benbouabdallah, M, Touhami, M, 1990, 'Epidemiology of juvenile insulin-dependent diabetes in Algeria (Wilaya of Oran)', *Rev Epidemiol Sante Publique*, **38**(2),91-99.

79. Vos, C, Reeser, HM, Hirasing, RA, Bruining, GJ, 1997, 'Confirmation of high incidence of type 1 (insulin-dependent) diabetes mellitus in Moroccan children in The Netherlands', *Diabet Med*, **14**(5), 397-400.

80. Elamin, A, Omer, MI, Zein, K, Tuvemo, T, 1992, 'Epidemiology of childhood type I diabetes in Sudan, 1987-1990', *Diabetes Care*, **15**(11), 1556-1559.

81. Elamin, A, Ghalib, M, Eltayeb, B, Tuvemo, T, 1997, 'High incidence of type I diabetes mellitus in Sudanese children, 1991-1995', *Ann Saudi Med*, **17**(4), 478-80.

82. Swai, AB, Lutale, JL, McLarty, DG, 1993, 'Prospective study of incidence of juvenile diabetes mellitus over 10 years in Dar es Salaam, Tanzania', BMJ, **306**(6892), 1570-2.

83. The Africa Diabetes Care Initiative (ADCI) 2010 – 2012, 2009, Diabetes in Africa: facing the future with hope for all ages, Retrieved on January 10, 2015, from http://www.idf.org/webdata/ADCI-2010-2012.

84. Samuelsson, U, Lofman, O, 2004, 'Geographical mapping of type 1 diabetes in children and adolescents in south east Sweden', *J Epidemiol Community Health*, **58**, 388-92.

85. Rytkonen, M, Ranta, J, Tuomilehto, J, Karvonen, M, 2001, 'Bayesian analysis of geographical variation in the incidence of Type I diabetes in Finland', *Diabetologia*, **44** Suppl 3, B37-44.

86. Cherubini, V, Carle, F, Gesuita, R, Iannilli, A, Tuomilehto, J, Prisco, F, Lafusco, D, Altobelli, E, Chairelli, F, DeGiorgi, G, Falorni, A, 1999, 'Large incidence variation of type I diabetes in central-southern Italy 1990-1995: lower risk in rural areas', *Diabetologia*, **42**, 789-92.

87. Songini, M, Bernardinelli, L, Clayton, D, Montomoli, C, Pascutto, C, Ghislandi, M, Fadda, D, Bottazzo, GF, 1998, 'The Sardinian IDDM study: 1. Epidemiology and geographical distribution of IDDM in Sardinia during 1989 to 1994', *Diabetologia,* **41**(2), 221-7.

88. Rytkonen, M, Moltchanova, E, Ranta , J, Taskinen, O, Tuomilehto, J, Karvonen, M, SPAT Study Group, Finnish Childhood Diabetes Registry Group, 2003, 'The incidence of type 1 diabetes among children in Finland-rural-urban difference', *Health Place*, **9**(4), 315-325.

89. Holmqvist, BM, Lofman, O, Samuelsson, U, 2008, 'A low incidence of Type 1 diabetes between 1977 and 2001 in south-eastern Sweden in areas with high population density and which are more deprived', *Diabet Med*, **25**(3), 255-60.

90. Patterson, CC, Carson, DJ, Hadden, DR, 1996, 'Epidemiology of childhood IDDM in Northern Ireland 1989-1994: low incidence in areas with highest population density and most household crowding, Northern Ireland Diabetes Study Group', *Diabetologia*, **39**(9), 1063-9.

91. Pundziute-Lycka, A, Urbonaite, B, Ostrauskas, R, Zalinkevicius, R, Dahlquist, GG, 2003, 'Incidence of type 1 diabetes in Lithuanians aged 0-39 years varies by the urban-rural setting, and the time change differs for men and women during 1991-2000', *Diabetes Care*, **26**(3), 671-6.

92. Ehehalt, S, Popovic, P, Muntoni, S, Willasch, A, Hub, R, Ranke, MB, Neu, A; DIARY Group Baden-Wuerttemberg, 2009, 'Incidence of diabetes mellitus among children of Italian migrants substantiates the role of genetic factors in the pathogenesis of type 1 diabetes', *Eur J Pediatr.*, **168**(5):613-617.

93. Moltchanova, EV, Schreier, N, Lammi, N, Karvonen, M, 2009, 'Seasonal variation of diagnosis of Type 1 diabetes mellitus in children worldwide', *Diabet. Med*, **26**(7), 673-678.

94. Kalliora, MI, Vazeou, A, Delis, D, Bozas, E, Thymelli, I, Bartsocas, CS, 2011, 'Seasonal variation of type 1 diabetes mellitus diagnosis in Greek children', *Hormones*, **10**(1), 67-71.

95. Padaiga, Z, Tuomilehto, J, Karvonen, M, Dahlquist, G, Podar, T, Adojaan, B, Urbonaite, B, Zalinkevicius, R, Brigis, G, Virtala, E, Kohtamäki, K, Cepaitis, Z, Tuomilehto-Wolf, E, 1999, 'Seasonal variation in the incidence of Type 1 diabetes mellitus during 1983 to 1992 in the countries around the Baltic Sea', *Diabet Med*, **16**(9), 736–743.

96. Douglas, S, McSporran, B, Smail, P, 'Seasonality of presentation of type I diabetes mellitus in children, Scottish Study Group for the Care of Young Diabetics', 1999, *Scott Med J*, **44**(2), 41–46.

97. Vaiserman, AM, Carstensen, B, Voitenko, VP, Tronko, MD, Kravchenko, VI, Khalangot, MD, Mechova, LV, 2007, 'Seasonality of birth in children and young adults (0–29 years) with type 1 diabetes in Ukraine', *Diabetologia*, **50**(1), 32–35.

98. McKinney, PA, EURODIAB Seasonality of Birth Group, 2001, 'Seasonality of birth in patients with childhood Type I diabetes in 19 European regions', *Diabetologia*, **44** (Suppl 3), B67-74.

99. Dahlquist, GG, Nystrom, L, Patterson, CC, The Swedish Childhood Diabetes Study group and The Diabetes Incidence in Sweden Group, 2011, 'Incidence of Type 1 Diabetes in Sweden Among Individuals Aged 0–34 Years, 1983–2007', *Diabetes Care*, **34**, 1754–1759.

100. Alemu, S, Dessie, A, Seid, E, Bard, E, Lee, PT, Trimble, ER, Phillips, DI, Parry, EH, 2009, 'Insulin-requiring diabetes in rural Ethiopia: should we reopen the case for malnutrition-related diabetes?,' *Diabetologia*, **52**(9),1842-1845.

101. Harjutsalo, V, Sjöberg, L, Tuomilehto, J, 2008, 'Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study', *Lancet*, **371**(9626):1777-82.

102. El-Ziny, MA1, Salem, NA, El-Hawary, AK, Chalaby, NM, and Elsharkawy, AA, 2014, 'Epidemiology of childhood type 1 diabetes mellitus in Nile Delta, northern Egypt - a retrospective study', *J Clin Res Pediatr Endocrinol*, **6**(1), 9-15.

103. Kalk, WJ, Huddle, KRL, Raal FJ, 1993, 'The age of onset and sex distribution of insulin-dependent diabetes mellitus in Africans in South Africa', *Postgrad Med J*, **69**(813), 552-556.

104. Afoke, AO, Ejeh, NM, Nwonu, EN, Okafor, CO, Udeh, NJ, Ludvigsson J, 1992, 'Prevalence and clinical picture of IDDM in Nigerian Igbo schoolchildren', *Diabetes Care*, **15**(10), 1310-1312.

105. Craig, ME, Jefferies, C, Dabelea, D, Balde, N, Seth, A, Donaghue, KC, 2014, 'Definition, epidemiology, and classification of diabetes in children and adolescents', *Pediatric Diabetes*, **15** (Suppl. 20): 4–17.

106. World Health Organization, 1999, Definition, diagnosis and classification of diabetes mellitus and its complications, Report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus, WHO/NCD/NCS/99.2, Geneva.

107. American Diabetes Association, 2015, 'Standards of medical care in diabetes – 2015: Position statement', *Diabetes Care*, **38**, (Suppl 1), S1-S93.

108. Couper, JJ, Haller, MJ, Ziegler, A-G, Knip, M, Ludvigsson, J, Craig, ME, 2014, 'Phases of type 1 diabetes in children and adolescents', *Pediatric Diabetes*, **15** (Suppl. 20), 18-25.

109. Craig, ME, Hattersley, A, Donaghue, KC, 2009, 'Definition, epidemiology and classification of diabetes in children and adolescents', Pediatric Diabetes, 10(suppl 12), 3–12.

110. Abdul-Rasoul, M, Habib, H, Al-Khouly, M, 2006, ''The honeymoon phase' in children with type 1 diabetes mellitus: frequency, duration, and influential factors', *Pediatric Diabetes*, **7**, 101–107.

111. Aly, H, and Gottlieb, P, 2009, 'The honeymoon phase: Intersection of metabolism and immunology', *Curr Opin Endocrinol Diabetes, and Obes*, **16**(4), 286-292.

112. Akirav, E, Kushner, JA, Herold, KC, 2008, 'Beta-cell mass and type 1 diabetes: Going, going, gone?', *Diabetes,* **57**(11), 2883–2888.

113. Lombardo, F1, Valenzise, M, Wasniewska, M, Messina, MF, Ruggeri, C, Arrigo, T, De Luca, F, 2002, 'Two-year prospective evaluation of the factors affecting honeymoon frequency and duration in children with insulin dependent diabetes mellitus: the key-role of age at diagnosis', *Diabetes Nutr Metab*, **15**(4), 246-51.

114. Bonfanti, R, Bognetti, E, Meschi, F, Brunelli, A, Riva, MC, Pastore, MR, Calori, G, Chiumello G, 1998, 'Residual beta cell function and spontaneous clinical remission in type 1 diabetes mellitus: the role of puberty', *Acta Diabetol*, **35**(2), 91–95.

115. Cryer, PE, 2012, 'Severe hypoglycemia predicts mortality in diabetes', *Diabetes Care*, **35**, 1814-1816.

116. The Diabetes Control and Complications Trial Research Group, 1993, 'The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus,' *N Engl J Med*, **329**(14), 977-986.

117. American Diabetes Association, 2014, 'Standards of medical care in diabetes – 2014: Position statement', *Diabetes Care*, **37**, (Suppl 1), S14-S80.

118. Borus, JS, Laffel, L, 2010, 'Adherence challenges in the management of type 1 diabetes in adolescents: prevention and intervention', *Curr Opin Pediatr*, **22**(4), 405–411.

119. Butler, DA, Zuehlke, JB, Tovar, A, Volkening, LK, Anderson, BJ, Laffel, LMB, 2008, 'The impact of modifiable family factors on glycaemic control among youth with type 1 diabetes', *Pediatric Diabetes*, **9**(4Part 2), 378–381.

120. Kim, H, Elmi, A, Henderson, CL, Cogen, FR, Kaplowitz, PB, 2012, 'Characteristics of children with type 1 diabetes and persistent suboptimal glycemic control', *J Clin Res Pediatr Endocrinol*, **4**(2), 82-88.

121. Hood, KK, Peterson, CM, Rohan, JM, Drotar, D, 2009, 'Association between adherence and glycemic control in pediatric type 1 diabetes: a meta-analysis', *Pediatrics*, **124**(6), e1171-9.

122. Silverstein, J, Klingensmith, G, Copeland, K, Plotnick, L, Kaufman, F, Laffel, L, Deep, L, Grey, M, Anderson, B, Holzmeister, LA, Clark, N, 2005, 'Care of children and adolescents with type 1 diabetes: A statement of the American Diabetes Association,' *Diabetes Care*, **28**(1), 186-212.

123. Nathan, DM, Cleary, PA, Backlund, JY, Genuth, SM, Lachin, JM, Orchard, TJ, Raskin, P, Zinman, B, The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group, 2005, 'Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes', *N Engl J Med*, **353**(25), 2643-2653.

124. American Diabetes Association, 2011, 'Standards of medical care in diabetes – 2011: Position statement', *Diabetes Care*, **34**, (Suppl 1), S11-S61.

125. Svensson, J, Johannesen, J, Mortensen, H, Nordly, S, 2008, 'Improved metabolic outcome in a Danish diabetec paediatric population aged 0 – 18 year: results from a nationwide continuous registration', *Pediatr Diabetes*, **10**(7), 461-7.

126. Majaliwa, ES, Munubhi, E, Ramaiya, K, Mpembeni, R, Sanyiwa A, Mohn A, 2007, 'Survey on acute and chronic complications in children and adolescents with type 1 diabetes at Muhimbili National Hospital in Dar es Salaam, Tanzania', *Diabetes Care*, **30**(9), 2187-92.

127. Gerstl, EM, Rabl, W, Rosenbauer, J, Gröbe, H, Hofer, SE, Krause, U, Holl, RW, 2008, 'Metabolic control as reflected by HbA1c in children, adolescents and young adults with type-1 diabetes mellitus: Combined longitudinal analysis including 27,035 patients from 207 centers in Germany and Austria during the last decade', *Eur J Pediatr*, **167**(4), 447-453.

128. Elbagir, MN, Eltom, MA, Rosling, H, Berne C, 1995, 'Glycaemic control of insulin-dependent diabetes mellitus in Sudan: influence of insulin shortage', *Diabetes Res Clin Pract.*, **30**(1), 43-52.

129. Formosa, N, 2013, 'Blood glucose monitoring in children and adolescents with type 1 diabetes mellitus', *Malta Med. Journal*, **25**(01), 31-35.

130. Haller, MJ, Stalvey, MS, Silverstein, JH, 2004, 'Predictors of control of diabetes: monitoring may be the key', *J Pediatr*, **144**, 660-661.

131. Chase, HP, Fiallo-Scharer, R, 2006, Chapter 7: Blood sugar (glucose) testing. In: Chase, HP editor, *Understanding diabetes: A handbook for people who are living with diabetes*, 11th ed, Children's Diabetes Foundation, Denver.

132. Miller, KM, Beck, RW, Bergenstal, RM, Goland, RS, Haller, MJ, McGill, JB, Rodriguez, H, Simmons, JH, Hirsch, IB; T1D Exchange Clinic Network, 2013, 'Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants', *Diabetes Care*, **36**(7), 2009-2014.

133. Ziegler, R, Heidtmann, B, Hilgard, D, Hofer, S, Rosenbauer, J, Holl, R; for the DPV-Wiss-Initiative, 2011, 'Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes', *Pediatric Diabetes*, **12**(1), 11–17.

134. Murata, T, Tsuzaki, K, Yoshioka, F, Okada, H, Kishi, J, Yamada, K, Sakane, N, 2015, 'The relationship between the frequency of self-monitoring of blood glucose and glycaemic control in patients with type 1 diabetes mellitus on continuous subcutaneous insulin infusion or on multiple daily injections', *J Diabetes Investig,* **6**(6),687–691.

135. Abdelgadir, M, Elbagir M, Eltom, M, Berne C, 2006, 'The influence of glucose self-monitoring on glycaemic control in patients with diabetes mellitus in Sudan', *Diabetes Res Clin Pract*., **74**(1), 90-94.

136. Patton, SR, Dolan, LM, Powers, SW, 2007, 'Dietary adherence and associated glycemic control in families of young children with type 1 diabetes', *J Am Diet Assoc*, **107**(1), 46-52.

137. Cuenca-García, M, Jago, R, Shield, JP, Burren, CP, 2012, 'How does physical activity and fitness influence glycaemic control in young people with Type 1 diabetes?', *Diabet Med,* **29**(10), e369-76. doi: 10.1111/j.1464-5491.2012.03740.x.

138. Miculis, CP, De Campos, W, da Silva Boguszweski, MC, 2015, 'Correlation between glycemic control and physical activity level in adolescents and children with type 1 diabetes', *J Phys Act Health*, **12**(2), 232-7.

139. Donaghue, KC, Chiarelli, F, Trotta, D, Allgrove, J, Dahl-Jorgensen, K, 2009, 'Microvascular and macrovascular complications associated with diabetes in children and adolescents', *Pediatric Diabetes*, **10** (Suppl. 12), 195–203.

140. Singh, VP, Bali, A, Singh, N, Jagg, AS, 2014, 'Advanced Glycation End Products and Diabetic Complications', *Korean J Physiol Pharmacol*, **18**(1), 1-14.

141. Nawale, RB, Mourya, VK, Bhise, SB, 2006, 'Non-enzymatic glycation of proteins: A cause for complications in diabetes', *Ind J Biochem Biophysics*, **43**, 337-344.

142. Beran, D, Yudkin, JS, 2006, 'Diabetes care in sub-Saharan Africa', *Lancet,* **368**(9548), 1689-95.

143. Sidibe, EH, 2000, 'Main complications of diabetes mellitus in Africa', *Ann Med Interne (Paris),* **151**(8), 624-8.

144. Usher-Smith, JA, Thompson, MJ, Sharp, SJ, Walter, FM, 2011, 'Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review', *BMJ,* **343**, 1-16.

145. Levy-Marchal, C, Patterson, CC, Green, A, 2001, Geographical variation of presentation at diagnosis of type I diabetes in children: the EURODIAB study, *Diabetologia*, **44** (Suppl 3), B75-80.

146. Ibekwe, MU, Ibekwe, RC, 2011, 'Pattern of type 1 diabetes mellitus in Abakaliki, Southeastern Nigeria', *Paediatric oncall*, **8**(7), Retrieved on August 25, 2015, from http://www.pediatriconcall.com/Journal/Article

147. Monabeka, HG, Mbika-Cardorelle, A, Moyen, G, 2003, 'Ketoacidosis in children and teenagers in Congo', *Sante*, **13**(3), 139-41.

148. Alanani, NMK Alsulaimani, AA, 2013, 'Epidemiological pattern of newly diagnosed children with type 1 diabetes mellitus Taif, Saudi Arabia', *Scientific World Journal*, **2013**, 1-9.

149. Razavi, Z, 2010, 'Frequency of ketoacidosis in newly diagnosed type 1 diabetic children', *OMJ*, **25**, 114-117.

150. Bui, TP, Werther, GA, Cameron FJ, 2002, 'Trends in diabetic ketoacidosis in childhood and adolescence: a 15-year experience', *Paediatr Diabetes*, **3**(2), 82-88.

151. Ly, TT, Maahs, DM, Rewers, A, Dunger, D, Oduwole, A, Jones, TW, 2014, 'ISPAD Clinical Practice Consensus Guidelines – Hypoglycemia: Assessment and management of hypoglycemia in children and adolescents with diabetes', *Pediatric Diabetes*, **15** (Suppl. 20), 180–192.

152. Cryer, PE, 2008, 'Hypoglycemia: still the limiting factor in the glycemic management of diabetes', *Endocr Pract*, **14**(6):750-756.

153. Tita, AT, Landon, MB, Spong, CY, Lai, Y, Leveno, KJ, Varner, MW, Moawad, AH, Caritis, SN, Meis, PJ, Wapner, RJ, Sorokin, Y, Miodovnik, M, Carpenter, M, Peaceman, AM, O'Sullivan, MJ, Sibai, BM, Langer, O, Thorp, JM, Ramin, SM, Mercer, BM, for the Eunice Kennedy Shriver NICHD Maternal–Fetal Medicine Units Network, 2009, 'Timing of elective repeat cesarean delivery at term and neonatal outcomes', *N Engl J Med*, **360**, 111-20.

154. Narchi, H, Skinner, A, 2009, 'Infants of diabetic mothers with abnormal fetal growth missed by standard growth charts', *J Obstet Gynaecol*, **29** (7), 609-613.

155. Ishiguro, A, Namai, Y, Ito YM, 2009, 'Managing "healthy" late preterm infants', *Pediatr Int,* **51**(5), 720-725.

156. Depuy, AM, Coassolo, KM, Som, DA, Smulian, JC, 2009, 'Neonatal hypoglycemia in term, nondiabetic pregnancies', *Am J Obstet Gynecol*, **200**(5), e45-51.

157. Obel, AO, 1983, 'Epidemiology of diabetes mellitus in a referral hospital in a tropical developing country', *Tohoku J Exp Med*, **141** Suppl: 207-10.

158. Krolewski AS, Quinn M, Krolewski, M, Quinn, M, Warram JH, 1995, 'Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus', *N Engl J Med*, **332**, 1251–1255.

159. Sharma, K, Ziyadeh, FN, 1995, 'Hyperglycaemia and diabetic kidney disease. The case for transforming growth factor-beta as a key mediator', *Diabetes Care*, **44**(10), 1139-46.

160. Mohsin, F, Craig, ME, Cusumano, J, Chan, AK, Hing, S, Lee, JW, Silink, M, Howard, NJ, Donaghue KC, 2005, 'Discordant trends in microvascular complications in adolescents with type 1 diabetes from 1990 to 2002', *Diabetes Care*, **28**(8), 1974-1980.

161. Schultz, CJ, Konopelska-Bahu, T, Dalton, RN, Carroll, TA, Stratton, I, Gale, EA, Neil, A, Dunger, DB, 1999, 'Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study. Oxford regional prospective study group', *Diabetes Care*, **22**(3), 495-502.

162. Amin, R, Widmer, B, Prevost, AT, Schwarze, P, Cooper, J, Edge, J, Marcovecchio, J, Neil, A, Dalton, RN, Dunger, DB, 2008, 'Risk of microalbuminuria and progression to macroalbuminuria in a cohort with childhood onset type 1 diabetes: Prospective observational study', *BMJ*, **336**(7646), 697-701.

163. Tabaei, BP, Al-Kassab, AS, Ilag, LL, Zawacki, CM Herman, WH, 2001, 'Does microalbuminuria predict diabetic nephropathy?', *Diabetes Care*, **24**(9), 1560-1566.

164. Perkins, BA, Ficociello, LH, Silva, KH, Finkelstein, DM, Warram, JH, Krolewski, AS, 2003, 'Regression of microalbuminuria in type 1 diabetes', *N Engl J Med*, **348**(23), 2285-2293.

165. Rossing, P, Hougaard, P, Parving, H-H, 2005, 'Progression of microalbuminuria in type 1 diabetes: Ten-year prospective observational study', *Kidney International*, **68**, 1446–1450.

166. Finne, P, Reunanen, A, Stenman, S, Groop, PH, Gronhagen-Riska, C, 2005, 'Incidence of end-stage renal disease in patients with type 1 diabetes', *JAMA*, **294**(14), 1782-1787.

167. Stanifer, JW, Jing, B, Tolan, S, Helmke, N, Mukerjee, R, Naicker, S, Patel, U, 2014, 'The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis', *Lancet Glob Health*, **2**, e174–181.

168. Sobngwi, E, Mbanya, JC, Moukouri, EN, Ngu, KB, 1999, 'Microalbuminuria and retinopathy in a diabetic population of Cameroon', *Diabetes Res Clin Pract*, **44**(3), 191-196.

169. de Zeeuw, D, Parving, H-H, Henning, RH, 2006, 'Microalbuminuria as an Early Marker for cardiovascular disease', *J Am Soc Nephrol*, **17**(8), 2100-2105.

170. Orchard, TJ, Costacou, T, Kretowski, A, Nesto, RW, 2006, 'Type 1 Diabetes and Coronary Artery Disease', Diabetes care, **29**(11), 2528- 2538.

171. Stephenson, JM, Kenny, S, Stevens, LK, Fuller, JH, Lee, E, 1995, 'Proteinuria and mortality in diabetes – The WHO Multinational Study of Vascular Disease in Diabetes', *Diabet Med*, **12**(2):149-55.

172. Mogensen, CE, Keane, WF, Bennett, PH, Jerums, G, Parving, HH, Passa, P, Steffes, MW, Striker, GE, Viberti, GC, 1995, 'Prevention of diabetic renal disease with special reference to microalbuminuria', *Lancet*, **346**(8982), 1080-1084.

173. Fong, DS, Aiello, LP, Ferris, FL, Klein, R, 2004, Diabetic retinopathy, *Diabetes Care*, **27**(10), 2540-2553.

174. Olsen, BS, Sjolie, A, Hougaard, P, Johannesen, J, Borch-Johnsen, K, Marinelli, K, Mortensen, HB, 2000, 'A 6-year nationwide cohort study of glycaemic control in young people with type 1 diabetes. Risk markers for the development of retinopathy, nephropathy and neuropathy. Danish study group of diabetes in childhood', *J Diabetes Complications*, **14**(6), 295-300.

175. Klein, R, Zinman, B, Gardiner, R, Suissa, S, Donnelly, SM, Sinaiko, AR, Kramer, MS, Goodyer, P, Moss, ES, Strand, T, Mauer, M, 2005, 'The relationship of diabetic retinopathy to preclinical diabetic glomerulopathy lesions in type 1 diabetic patients: The renin-angiotensin system study', *Diabetes*, **54**(2), 527-533.

176. Jingi, AM, Noubiap, JJN, Ellong, A, Bigna, JJR, Mvogo, CE, 2014, 'Epidemiology and treatment outcomes of diabetic retinopathy in a diabetic population from Cameroon', *BMC Ophthalmology*, **14**(19), 1-5.

177. Daneman, D, 2006, 'Type 1 diabetes', *Lancet*, **367**(9513), 847-858.

178. Eeg-Olofsson, K, Cederholm, J, Nilsson, PM, Gudbjornsdottir, S, Eliasson, B, Steering Committee of the Swedish National Diabetes Register, 2007, 'Glycemic and risk factor control in type 1 diabetes: Results from 13,612 patients in a national diabetes register' *Diabetes Care*, **30**(3), 496-502.

179. Katzmarzyk, PT, Srinivasan, SR, Chen, W, Malina, RM, Bouchard, C, Berenson, GS, 2004, 'Body mass index, waist circumference, and clustering of cardiovascular disease risk factors in a biracial sample of children and adolescents' *Pediatrics*, **114**(2), e198-205.

180. McGill, HCJr, McMahan, CA, Herderick, EE, Zieske, AW, Malcom, GT, Tracy RE, Strong, JP; Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group, 2002, 'Obesity accelerates the progression of coronary atherosclerosis in young men', *Circulation*, **105**(23), 2712-2718.

181. Barton, M, 2012, 'Childhood obesity: a life-long health risk', *Acta Pharmacologica Sinica*, **33**, 189-193.

182. Krishnan, S, Short, KR, 2009, 'Prevalence and significance of cardiometabolic risk factors in children with type 1 diabetes', *J Cardiometabolic Syndrome*, **4**(1), 50-56.

183. van Vliet, M, Van der Heyden, JC, Diamant, M, Von Rosenstiel, IA, Schindhelm, RK, Aanstoot, HJ, Veeze, HJ, 2010, 'Overweight is highly prevalent in children with type 1 diabetes and associates with cardiometabolic risk', *J Pediatrics*, **156**(6), 923-929.

184. Margeirsdottir, HD, Larsen, JR, Brunborg, C, Overby, NC, Dahl-Jørgensen, K; Norwegian Study Group for Childhood Diabetes, 2008, 'High prevalence of cardiovascular risk factors in children and adolescents with type 1 diabetes: a population-based study', *Diabetologia*, **51**(4), 554-61.

185. Rodriguez, BL, Fujimoto, WY, Mayer-Davis, EJ, Imperatore, G, Williams, DE, Bell, RA, Wadwa, RP, Palla, SL, Liu, LL, Kershnar, A, Daniels, SR, Linder, B, 2006, 'Prevalence of cardiovascular disease risk factors in U.S. children and adolescents with diabetes: The SEARCH for diabetes in youth study', *Diabetes Care*, **29**(8), 1891-1896.

186. Tesfaye, S, Gill, G, 2011, 'Chronic diabetic complications in Africa', *African J Diab Med*, **19**(1), 1-8.

187. Kengne, AP, Amoah, AGB, Mbanya, JC, 2005, 'Cardiovascular complications of diabetes mellitus in Sub-Saharan Africa', *Circulation*, **112**, 3592-3601.

188. Tamba, SM, Ewane, ME, Bonny, A, Muisi, CN, Nana, E, Ellong, A, Mvogo, CE, Mandengue, SH, 2013, 'Micro and macrovascular complications of diabetes mellitus in Cameroon: risk factors and effect of diabetic check-up - a monocentric observational study', *PanAfrican Med J*, **15**(141), 1-10.

189. Nathan, DM, Cleary, PA, Backlund, J-YC, Genuth, SM, Lachin, JM, Orchard, TJ, Raskin, P, Zinman, B, The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group, 2005, 'Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes', *New Engl J Med*, **353**(25), 2643-2653.

190. Secrest, AM, Coustacou, T, Gutelius, B, Miller, RG, Songer, TJ, Orchard, TJ, 2011, 'Associations between Socioeconomic Status and Major Complications in Type 1 Diabetes: The Pittsburgh Epidemiology of Diabetes Complication (EDC) Study', *Ann Epidemiol*., **21**(5), 374–381.

191. Petitti, DB, Klingensmith, GJ, Bell, RA, Andrews, JS, Dabelea, D, Imperatore, G, Marcovina, S, Pihoker, C, Standiford, D, Waitzfelder, B, Mayer-

Davis, E, 2009, 'Glycemic Control in Youth with Diabetes: The SEARCH for Diabetes in Youth Study', *J Pediatr*, **155**(5), 668-672.

192. Clements, MA, Lind, M, Raman, Patton, SS, Lipska, KJ, Fridlington, AG, Tang, F, Jones, PG, Wu, Y, Spertus, JA, Kosiborod, M, 2014, 'Age at diagnosis predicts deterioration in glycaemic control among children and adolescents with type 1 diabetes', *BMJ Open Diab Res Care*, **2**, e000039. doi:10.1136/bmjdrc-2014-000039.

193. McKinney, PA, Feltbower, RG, Stephenson, CR, Reynolds, C, 2008, 'Children and young people with diabetes in Yorkshire: a population-based clinical audit of patient data 2005/2006', *Diabet Med*, **25**(11), 1276-82.

194. O'Hagan, M, Harvey, JN, for the Brecon Group, 2010, 'Glycemic control in children with type 1 diabetes in Wales', *Diabetes care*, **3**, 1724–1726.

195. Carter, PJ, Cutfield, WS, Hofman, PL, Gunn, AJ, Wilson, DA, Reed, PW, 2008, 'Ethnicity and social deprivation independently influence metabolic control in children with type 1 diabetes', *Diabetologia*, **51**(10), 1835-42.

196. Craig, ME, Handelsman, P, Donaghue, KC, Chan, A, Blades, B, Laina, R, 2002, 'Predictors of glycaemic control and hypoglycaemia in children and adolescents with type 1 diabetes from NSW and the ACT', *Med J Aust*, **177**(5), 235-238.

197. Rosilio, M, Cotton, JB, Wieliczko, MC, Gendrault, B, Carel, JC, Couvaras, O, Ser, N, Gillet, P, Soskin, S, Garandeau, P, Stuckens, C, Le Luyer, B, Jos, J, Bony-Trifunovic, H, Bertrand, AM, Leturcq, F, Lafuma, A, French Pediatric Diabetes Group, Bougnères, PF, 1998, 'Factors associated with glycemic control. A cross-sectional nationwide study in 2,579 French children with type 1 diabetes. The French Pediatric Diabetes Group', *Diabetes Care*, **21**(7), 1146-53.

198. Majidi, S, Wadwa, RP, Bishop, FK, Klingensmith, GJ, Rewers, M, McFann, K, Maahs, DM, 2014, 'The effect of insurance status and parental education on glycemic control and cardiovascular disease risk profile in youth with Type 1 Diabetes', *J of Diab & Metab Dis*, **13**(59), 1-4.

199. Springer, D, Dziura, J, Tamborlane, WV, Steffen, AT, Ahern, JH, Vincent, M, Weinzimer, SA, 2006, 'Optimal control of type 1 diabetes mellitus in youth receiving intensive treatment', *J Pediatr*,**149**, 227-32.

200. Cutfield, SW, Derraik, JGB, Reed, PW, Hofman, PL, Jefferies, C, Cutfield, WS, 2011, 'Early Markers of Glycaemic Control in Children with Type 1 Diabetes Mellitus', *PLoS ONE*, **6**(9), e25251. doi:10.1371/journal.pone.0025251.

201. Overstreet, S, Holmes, CS, Dunlap, WP, Frentz, J, 1997, 'Sociodemographic risk factors to disease control in children with diabetes', *Diabet Med.*, **14**(2), 153-157.

202. Mohammad, HA, Farghaly, HS, Metwalley, KA, Monazea, EM, Abd El-Hafeez, HA, 2012, 'Predictors of glycemic control in children with Type 1 diabetes mellitus in Assiut-Egypt', *Indian J Endocr Metab*, **16**(5), 796-802.

203. Galler, A, Lindau, M, Ernert, A, Thalemann, R, Raile, K, 2011, 'Associations Between Media Consumption Habits, Physical Activity, Socioeconomic Status, and Glycemic Control in Children, Adolescents, and Young Adults With Type 1 Diabetes', *Diabetes Care*, **34**(11), 2356-2359.

204. Cameron, FJ, Skinner, TC, de Beaufort, CE, Hoey, H, Swift, PGF, Aanstoot, H, Åman, J, Martul, P, Chiarelli, F, Daneman, D, Danne, T, Dorchy, H, Kaprio, EA, Kaufman, F, Kocova, M, Mortensen, HB, Njølstad, PR, Phillip, M, Robertson, KJ, Schoenle, EJ, Urakami, T, Vanelli, M, Ackermann, RW, Skovlund, SE, for and on behalf of the Hvidoere Study Group on Childhood Diabetes, 2008, 'Are family factors universally related to metabolic outcomes in adolescents with Type 1 diabetes?', *Diabet. Med.*, **25**, 463–468.

205. Thompson, SJ, Auslander, WF, White, NH, 2001, 'Comparison of single-mother and two-parent families on metabolic control of children with diabetes', *Diabetes Care*, **24**(2), 234-8.

206. Anderson, BJ, Vangsness, Connell, LA, Butler, D, Goebel-Fabbri, A, Laffel, LMB, 2002, 'Family conflict, adherence, and glycaemic control in youth with short duration Type 1 diabetes', *Diabet. Med.*, **19**(8), 635–642.

207. Anderson, B, Ho J, Brackett, J, Finkelstein, D, Laffel, L, 1997, 'Parental involvement in diabetes management tasks: relationships to blood glucose monitoring adherence and metabolic control in young adolescents with insulin-dependent diabetes mellitus', *J Pediatr.*, **130**(2), 257-265.

208. Pereira, MG, Berg-Cross, L, Almeida, P, Machado, JC, 2008, 'Impact of family environment and support on adherence, metabolic control, and quality of life in adolescents with diabetes', *Int J Behav Med.*, **15**(3), 187-193.

209. Tsiouli, E, Alexopoulos, EC, Stefanaki, C, Darviri, C, Chrousos, GP, 2013, 'Effects of diabetes-related family stress on glycaemic control in young patients with type 1 diabetes', *Can Fam Physician*, **59,** 143-149.

210. Cardwell, CR, Patterson, CC, Allen, M, Carson, DJ, on behalf of the Northern Ireland Paediatric Diabetes Study Group, 2005, 'Diabetes care provision and glycaemic control in Northern Ireland: a UK regional audit', *Arch Dis Child*, **90**, 468–473.

211. Kaufman, FR, Halvorson, M, Carpenter, S, 1999, 'Association between diabetes control and visits to a multidisciplinary pediatric diabetes clinic', *Pediatrics*, **103**, 948-951.

212. Urbach, SL, LaFranchi, S, Lambert, L, Lapidus, JA, Daneman, D, Becker, TM, 2005, 'Predictors of glucose control in children and adolescents with type 1 diabetes mellitus', *Pediatric Diabetes*, **6**, 69-74.

213. Mehta, SN, Volkening, LK, Anderson, BJ, Nansel, T, Weissber-Benchell, J, Wysocki, T, Laffel, LMB, for the Family Management of Childhood Diabetes Study steering Committee, 2008, 'Dietary behaviors predict glycemic control in youth with type 1 diabetes', *Diabetes Care*, **31**(7), 1318–1320.

214. Al-Odayani, AN, Alsharqi, OZ, Ahmad, AMK, Al-Asmari, AK, Al-Borie, HM, Qattan, AMN, 2013, 'Children's Glycemic Control: Mother's Knowledge and Socioeconomic Status', *Global Journal of Health Sciences*, **5**(6), 214-226.

215. Pendley, JS, Kasmen LJ, Miller DL, Donze J, Swenson C, Reeves G, 2002, 'Peer and family support in children and adolescents with type 1 diabetes', *J Pediatr Psychol.* **27**(5), 429-38.

216. Pulgarón, ER, Sanders, LM, Patiño-Fernandez, AM, Wile, D, Sanchez, J, Rothman, RL, Delamater, AM, 2014, 'Glycemic control in young children with diabetes: the role of parental health literacy', *Patient Educ Couns*, **94**(1), 67-70.

217. Tahirovic, H, Toromanovic, A, 2010, 'Glycemic control in diabetic children: role of mother's knowledge and socioeconomic status', *Eur J Pediatr.*, **169**(8), 961-964.

218. Stallwood, L, 2006, 'Relationship between caregiver knowledge and socioeconomic factors on glycemic outcomes of young children with diabetes, *J Spec Pediatr Nurs.*, **11**(3), 158-65.

219. Soheilipour, F, Jolfaei, AG, Khodapanahandeh, F, Rajab, A, Salehiniya, H, Asoudegi, M, Tamannaie, Z, Rahimzadeh, N, 2015, 'The Relationship Between Maternal Awareness, Socioeconomic Situation of Families and Metabolic Control in Children With Type 1 Diabetes Miletus in an Iranian Population', *J Compr Ped*, **6**(3): e26924. DOI: 10.17795

220. Hassan, K, Heptulla, RA, 2009, 'Glycemic control in pediatric type 1 diabetes: Role of caregiver literacy', *Pediatrics*, **125**, e1104–e1108.

221. Vimalavathini, R, Agarwal, SM, Gitanjali, B, 2008, 'Educational program for patients with type-1 diabetes mellitus receiving free monthly supplies of insulin improves knowledge and attitude, but not adherence', *Int J Diabetes Dev Ctries*., **28**(3), 86-90.

222. Halvorson, M, Yasuda, P, Carpenter, S, Kaiserman, K, 2005, 'Unique challenges for pediatric patients with diabetes', *Diabetes Spectrum*, **18**(3), 167-173.

223. Majaliwa, ES, Elusiyan, BE, Adesiyun, OO, Laigong, P, Adeniran, AK, Kandi, CM, Yarhere, I, Limbe, SM, Iughetti, L, 2008, 'Type 1 diabetes mellitus in the African population: epidemiology and management challenges', *Acta Biomed*, **79**(3), 255-259.

224. Ghannem, H, Harrabi, I, Gaha, R, Trabelsi, L, Chouchene, I, Essoussi, AS, Ammar, H, 2001, 'Epidemiology of diabetes in a school children population in Tunisia', *Diabetes Metab*, **27**(5 Pt 1):613-617.

225. Dham, S, Shah, V, Hirsch, S, and Banerji, MA, 2006, 'The role of complementary and alternative medicine in diabetes', *Curr Diab Rep***, 6**(3), 251-258.

226. Adeleke, SI, Asani, MO, Belonwu, RO, Gwarzo, GD, Farouk, ZL, 2010, 'Childhood diabetes mellitus in Kano, North West Nigeria', *Nig J Med*, **19**(2), 145-147.

227. Institut National de la Statistique. La population du Cameroun en 2010. Retrieved on September 12, 2015, from http://www.statisticcameroon.org/downloads/La_population_du_Cameroon.

228. Pasquet, P, Temgoua, LS, Melaman-Sego, F, Fromentz, A, Rikong-Andie, A, 2003, 'Prevalence of overweight and obesity for urban adults in Cameroon' *Annals of Human Biology*, **30**(5), 551 – 562.

229. Hsieh, FY, Bloch, DA, Larsen, MD, 1998, 'A simple method of sample size calculation for linear and logistic regression', *Statist. Med.*, **17**, 1623-1634.

230. Hsieh, FY, 1989, 'Sample size tables for logistic regression', *Statist. Med.*, **8**, 795-802.

231. Fezeu, LK, Assah, FK, Balkau, B, Mbanya, DS, Kengne, AP, Awah, PK, Mbanya, JCN, 2008, 'Ten-year changes in central obesity and BMI in rural and urban Cameroon' *Obesity*, **16**, 1144–1147.

232. Fitzgerald, JT, Funnell, MM, Hess, GE, Barr, PA, Anderson, RM, Hiss RG, 1998, 'The reliability and validity of a brief diabetes knowledge test', *Diabetes Care*, **21**(5), 706-710.

233. Geissler, CA, Powers, H, 2005, *Human Nutrition*, 11th edition, Churchill Livingstone, London.

234. Cole, TJ, Bellizzi, MC, Flegal, KM, Dietz, WH, 2000, 'Establishing a standard definition for child overweight and obesity worldwide: international survey', *British Medical Journal*, **320**(7244), 1240-1243.

235. Borghi, E, Garza, C, Van den Broeck, J, Frongillo, EA, Grummer, L, Van Buuren, S, Molinari, L, Martorell, R, Onyango, AW, Martines, JC, 2006, 'Construction of World health Organisation child growth standards: selection of methods for attained growth curves', *Statist Med*, **25**, 247 – 265.

236. Ngwiri, T, Were F, Predieri B, Ngugi P, Iughetti L, 2015, 'Glycaemic control in Kenyan children and adolescents with type 1 diabetes mellitus', *International Journal of Endocrinology*, **2015**, 1-7.

237. Pillay, K, Maunder, EMW, Naidoo, KL, 2009, 'Dietary intake and metabolic control in children aged six to ten with type 1 diabetes in KwaZulu-Natal', *S Afr J Clin Nutr*, **22**(2), 95-98.

238. Gallegos-Macias, AR, Macias, SR, Kaufman, E, Skipper B, Kalishman, N, 2003, 'Relationship between glycaemic control, ethnicity and socioeconomic status in Hispanic and white non-Hispanic youths with type 1 diabetes mellitus', *Pediatric Diabetes*, **4**,19-23.

239. Hassan, K, Loar, R, Anderson, BJ, Heptulla, RA, 2006, 'The role of socioeconomic status, depression, quality of life and glycaemic control in type 1 diabetes mellitus', *J Pediatr*, **149**,526-531.

240. Frey, MA, Templin, T, Ellis, D, Gutai J, Podolski, C-L, 2007, 'Predicting metabolic control in the first 5 year after diagnosis for youths with type 1 diabetes: the role of ethnicity and family structure', *Pediatric Diabetes*, **8**, 220–227.

241. Araujo, MB, Mazza, CS, 2008, 'Assessment of risk factors of poor metabolic control in type 1 diabetic children assisted in a public hospital in Argentina', *Pediatric Diabetes*, **9,** 480–487.

242. Jacobson, AM, Hauser, ST, Willett, J, Wolfsdorf, JI, Herman, L, 1997, 'Consequences of irregular versus continuous medical follow-up in children and adolescents with insulin-dependent diabetes mellitus', *J Pediatr.*, **131**(5), 727-33.

243. Berg, CA, King, PS, Butler, JM, Pham, P, Palmer, D, Wiebe, DJ, 2010, 'Parental involvement and adolescents' diabetes management: The mediating role of self-efficacy and externalizing and internalizing behaviors', *Journal of Pediatric Psychology*, **36**(3), 329–339.

244. Lewin, AB, Heidgerken, AD, Geffken, GR, Williams, LB, Storch, EA, Gelfand, KM, Silverstein, JH, 2006, 'The relation between family factors and glycemic control: The role of diabetes adherence', *Journal of Pediatric Psychology*, **31**, 174–183.

245. Sweenie, R, Mackey, ER, Streisand, R, 2014, 'Parent-child relationships in type 1 diabetes: Associations among child behavior, parenting behavior, and pediatric parenting stress', *Fam Syst Health*, **32**(1), 31–42.

246. Anderson, BJ, Holmbeck, G, Iannotti, RJ, Mackay, SV, Lochrie, A, Volkening, LK, Laffel, L, 2009, 'Dyadic measures of the parent–child relationship during the transition to adolescence and glycemic control in children with type 1 diabetes', Families, Systems, & Health, **27**(2), 141–152.

247. Onyiriuka, AN, Ifebi, E, 2013, 'Ketoacidosis at diagnosis of type 1 diabetes in children and adolescents: frequency and clinical characteristics', *Journal of Diabetes & Metabolic Disorders*, **12**:47, doi: 10.1186/2251-6581-12-47.

248. Neu, A, Hofer, SE, Karges, B, Oeverink, R, Rosenbauer, J, Holl, RW, for the DPV Initiative and the German BMBF competency network for diabetes mellitus, 2009, 'Ketoacidosis at diabetes onset is still frequent in children and adolescents', *Diabetes Care*, **32**(9), 1647–1648.

249. Fritsch, M, Rosenbauer, J, Schober, E, Neu, A, Placzek, K, Holl, RW, 2011, 'Predictors of diabetic ketoacidosis in children and adolescents with type 1 diabetes', *Pediatric Diabetes*, **12**, 307–312.

250. Wolfsdorf, J, Craig, M, Daneman, D, Dunger, D, Edge, J, Lee, W, Rosenbloom, A, Sperling, M, Hanas, R, 2009, 'ISPAD clinical practice consensus guidelines 2009 compendium: Diabetic ketoacidosis in children and adolescents with diabetes', *Pediatr Diabetes*, **10**(Suppl 12), 118–133.

251. Jaser, SS, 2010, 'Psychological problems in adolescents with diabetes', *Adolesc Med State Art Rev*., **21**(1), 138–xi.

252. Jack, L, Jr., 2003, 'Biopsychosocial factors affecting metabolic control among female adolescents with type 1 diabetes', *Diabetes Spectrum*, **16**(3), 154-159.

253. Hassan, K, Loar, R, Anderson, BJ, Heptulla, RA, 2006, 'The role of socioeconomic status, depression, quality of life, and glycemic control in type 1 diabetes mellitus', *J Pediatr*., **149**(4), 526-31.

254. Hapunda, G, Abubakar, A, van de Vijver, F, Pouwer, F, 2015, 'Living with type 1 diabetes is challenging for Zambian adolescents: qualitative data on stress, coping with stress and quality of care and life', *BMC Endocr Disord*, **15** (20), DOI 10.1186/s12902-015-0013-6.

255. Hill, AB, 1965, 'The environment and disease: association or causation?', *Proc R Soc Med*., **58,** 295-300.

256. Leininger, MM, 1991, Culture care diversity and universality: A theory of nursing: *In Nursing Theories; the base for professional nursing practice*, Appleton and Lange, Norwalk Connecticut.

257. Papadopuolous, I, Tilki, M, Taylor, G, 1998, *Transcultural care: A Guide for Healthcare Professionals*, Wilts: Quay books.

258. Giger, JN, Darvidhizar, RE, 2008, *Transcultural Nursing Assessment and Intervention*, 5th edn, Mosby.

259. Galobardes, B, Morabia, A, Bernstein, MS, 2001, 'Diet and socioeconomic position: does the use of different indicators matter?', *International Journal of Epidemiology*, **30**, 334 – 340.

260. Fezeu, L, Minkoulou, E, Balkau, B, Kengne, AP, Awah, P, Unwin, N, Alberti, GK, Mbanya, JC, 2005, 'Association between socioeconomic status and adiposity in urban Cameroon', *International Journal of Epidemiology*, **35**, 105 – 111.

7. Curriculum Vitae

Loveline Lum Niba

Work address: Department of Biochemistry, Catholic University of Cameroon (CATUC), Bamenda. P.O. Box 782, Bamenda, North West Region, Cameroon
Mobile: +237674846150, Email: Niba.Loveline@lrz.uni-muenchen.de

University: University of Buea, Cameroon
London Metropolitan University, UK
Ludwig-Maximilians-Universität (LMU), Munich, Germany

Qualifications:

1998	BSc. (*Hons*) Biochemistry
2007	MSc. Biochemistry
2009	MSc. Medical Genetics

Positions:

1998-2004	Science Teacher, English High School, Yaounde, Cameroon
04/2007 - 12/2007	Graduate Assistant, University of Buea, Cameroon
	Health Educator, Fobang Foundation, Yaounde
01/2008 - 08/2008	Assistant Lecturer, Department of Biochemistry,
10/2010 - present	Catholic University of Cameroon, Bamenda

Awards:

- 1998 Ministry of Higher Education Meritorious Award as the best female scientist in the University of Buea, Cameroon.
- 2004 Graduate Scholarship from the Melford Charity Trust, UK to pursue an MSc. in Biochemistry at the University of Buea, Cameroon
- 2013 Service Award: Catholic University of Cameroon, Bamenda
- 2013 PhD scholarship, Center for International Health at LMU
- 2015 International Diabetes Federation fellow

Professional affiliations: Registered member of the British Society for Human Genetics and the Cameroon Diabetes Association

Languages: Working knowledge of French, understands basic German

8. LIST OF PUBLICATIONS

Research article

Under review:

Niba, LL, Aulinger, B, Mbacham, WF, Parhofer, KG, Predictors of glucose control in children and adolescents with type 1 diabetes: results of a cross-sectional study in Cameroon. Submitted to *BMC Research Notes*.

Abstract

Published:

Niba, L, Aulinger, B, Mbacham, W, Parhofer, K, Determinants of outcome of children with type 1 diabetes in Cameroon. Abstracts of the 54th Annual Meeting of the European Society for Paediatric Endocrinology (ESPE), Barcelona, Spain. *Hormone Research in Paediatrics*, **82** (Suppl 1); p185, 2015. Retrieved from http://abstracts.eurospe.org/hrp/0084/hrp0084p2-276.htm.

9. APPENDIX

APPENDIX 1: Parent Questionnaire

Please complete all the questions on this questionnaire which will take about 30 minutes of your time

Patient code [ ]

SOCIODEMOGRAPHIC DATA AND BACKGROUND INFORMATION

1. Telephone contact _____
2. Residence_____
3. What is your child's date of birth (day/month/year): _____
4. When was your child diagnosed of diabetes (day/month/year):_____
5. What was your child`s age at diagnosis of diabetes mellitus?_____
6. What is your child`s body weight (Kg) _____
7. What is the height of your child (m) _____
8. For how long have your child been living with diabetes? _____
9. Primary caregiver (Please circle the right answer) Example: a. (Mother) b. Father
   a. Mother b. Father c. Brother/Sister d. Other – specify _____
10. What is your child`s insulin regimen: (Please circle the right answer).
    a. Multiple daily insulin injections b. 2 daily insulin injections
11. What is the highest level of education completed by the primary caregiver of your child? (circle the right answer):
    a. No formal education b. Primary c. Secondary d. High school e. University
12. What is your family structure (select one and circle the right answer):
    a. Both parents are living together b. Single parent family c. Not living with either parent d. Orphan
13. Is there any other member of your family suffering from type 1 or type 2 diabetes? (circle the right answers)
    a. Mother b. Brother/Sister c. father d. Uncle/Aunt e. Grandparent f. None

14. At the time of diagnosis did your child have any of the following; (Circle the right answer)
    - Ketones in the urine a. Yes b. No
    - Altered consciousness or coma a. Yes b. No
15. How many times have your child been found to have the following in the last 6 months?

    -Presence of ketones in urine_____

    -Weakness or sweating or vomiting_____

    -Admission to hospital over the last 6 months_____
16. Does your child suffer from any of the following? (Circle the right answers).
    a. Dizziness b. Poor memory c. Lack of energy d. Coma/Convulsion
17. How many times have your child experienced any of the above during the last 6 months _____
18. Did your child suffer from any of the following when he/she was young? (Circle the right answers!)
    a. Measles b. Weight loss c. Eczema d. weakness e. Mumps f. Diarrhea h. none
19. Was your child suffering from any of the following at the time of diagnosis? (Circle the right answers!)
    a. Cold b. coma c. weakness d. stomach problems e. Weight loss

    f. weakness g. none

    For how long did your child suffer from it before being diagnosed of diabetes? ____

20. **Socioeconomic status (circle the right answer)**

MOTHER	FATHER
1-Number of children	1- Number of children
2-What is your highest level of education? Please tick one! a. None b. Primary c. Secondary d. High School e. University	2- What is your highest level of education? Please tick one a) None b. Primary c. Secondary d. High School e. University
3-What is your occupation?	3-What is your occupation?
4-Can you give an estimate of your household income in a month (from all available sources) Please tick one. a) Below 25,000frs b) 25,000frs - 50,00frs c) 50,000frs - 100,000frs d) 100,000frs - 200,000frs e) 200,000frs – 300,000frs f) 300,000frs – 400,000frs g) 400,000frs and above	4-Can you give an estimate of your household income in a month (from all available sources) Please tick one. a) Below 25,000frs b) 25,000frs - 50,00frs c) 50,000frs - 100,000frs d) 100,000frs - 200,000frs e) 200,000frs – 300,000frs f) 300,000frs – 400,000frs g) 400,000frs and above
5- What is your religion? a. None b. Catholic c. Protestant d. Muslim e. Other……	5- What is your religion? a. None b. Catholic c. Protestant d. Muslim e. Other……

I. DIABETES KNOWLEDGE ASSESSMENT

(Assessed using the Michigan Diabetes Research and Training Center's brief diabetes knowledge test)

A. DIABETES KNOWLEDGE ASSESSMENT OF CAREGIVERS: (Please tick the right answer)

1. Which of the following is highest in carbohydrates?
   a. Chicken b. Fish c. Potato d. Butter
2. Which of the following is highest in fats?
   a. Milk b. Orange juice c. Maize d. Honey
3. Which is the best method for testing your child's glucose?

a. Urine testing b. Blood testing c. Both are equally good

4. What effect does unsweetened fruit juice have on your child's blood glucose?
   a. It lowers blood glucose b. It raises blood glucose c. It has no effect on blood glucose
5. What effect does exercise have on the level of blood glucose?
   a. It raises blood glucose b. It lowers blood glucose c. It has no effect on blood glucose
6. Having an infection is likely to cause which of the following?
   a. A decrease in the blood glucose b. An increase in the blood glucose c. No change in the blood glucose
7. Tingling and numbness may be symptoms of which of the following?
   a. Eye disease b. Nerve disease c. Kidney disease d. Liver disease
8. Which of the following is usually not associated with diabetes?
   a. Nerve problems b. Lung problems c. Eye problems d. Kidney problems
9. Signs of ketoacidosis (very high blood sugar) include:
   a. Shakiness b. Sweating c. Vomiting
10. If your child is sick with the flu, which of the following changes would you tell her/him to make?
    a. Take less insulin b. Drink less liquids c. Eat more proteins d. Test for blood glucose more often
11. You realize just before lunch time that your child forgot to take his/her insulin before breakfast. What should you advise him to do now?
    a. Skip lunch to lower blood glucose
    b. Take the insulin that he/she usually takes at breakfast
    c. Take twice as much insulin as he/she usually takes at breakfast
    d. Check his/her blood glucose level to decide how much insulin to take
12. Low blood glucose may be caused by which of the following?
    a. Too little insulin b. Too much insulin c. Too much food d. Too little exercise

13. If your child takes morning insulin but skips breakfast, his/her blood glucose level will usually:
    a. Increase b. Decrease c. Remain the same
14. High blood glucose may be caused by:
    a. Not enough insulin
    b. Skipping meals
    c. Delaying your food
15. Glycosylated haemoglobin (haemoglobin A 1) is a test that is a measure of your average blood glucose level for the past:
    a. Day b. Week c. 3 months d. 6 months
16. What was your child`s last HbA1c level? _____

II. DIABETES RELATED PRACTICES OF PATIENT/CAREGIVER

1. Is there anybody at the clinic/health centre that your child can contact in case of any problems for advice? a) Yes b) No
2. Was your child given clear instructions on how to handle his/her dose of insulin or inject your insulin? a) Yes b) No

1. How many doses of insulin have your child missed in the last one week?
    a) None b) Between 1 – 3 times c) More than 3 times
2. How many times have your child measured his/her blood glucose at home in the last one week?
    a) Every day b) More than or 3 times a week c) 1 – 2 times a week d) less than Once a week
3. What did your child eat in the last 24 hours?
    During breakfast _____
    For lunch _____
    During supper _____
    Any snacks? (How many times?) _____
4. How does your child store his/her insulin? a) Refrigerator b) Pot of cold water c) Room temperature

5. In the last 24 hours, how many times did the parent/caregiver inject or supervise the insulin injection of his/her child?

a) None b) Once or twice c) All the injections

7. How involved is the parent/caregiver in the testing/measurement of his/her child`s blood glucose? Please tick!

a) No involvement

b) Reminds the child to monitor glucose or logs in the level in the diary or asks about the blood glucose level

c) Sets up the meter and does the finger prick

8. How many times did your child visit the doctor/clinic during the last 6 months?

a) None b) Between 1-3 times c) More than 3 times

9. Have your child been admitted to the hospital over the last year? a) Yes b) No. **If the answer is Yes**

-How many times? _____

-How many days? _____

-What was the reason for your child's admission _____

III: AVAILABILITY OF INSULIN

1. In the last 3 months, have your child ever missed getting his/her prescribed insulin from the hospital? a) Yes b) No

2. If **Yes,** how frequently have your child missed his/her supplies?

a) Every month b) Once or twice in 3 months

3. When your child misses his/her supplies of insulin or syringes, what does he/she usually do?

a) Buy his/her own insulin b) Wait till supplies of insulin are available from the hospital

IV: THE IMPACT OF DIABETES ON DAILY LIFE AND LOCAL FACTORS

1. Does your child frequently miss school due to diabetes and related complications?

a) Yes b) No If **Yes,** in the last 1 month, how many missed days of school? ___

2. Does having diabetes affect your child`s performance in school? a)Yes b) No
3. Does having diabetes restrict your child from regular sports? a)Yes b) No
   If **No**, how many times do you do sports a week? _____
4. Does having diabetes cause your child to isolate him/herself from friends?
   a) Yes b) No
5. Does having diabetes sometimes make your child unhappy? a)Yes b) No
6. Has having diabetes had a positive impact on the life of your child? a) Yes b) No
   If **Yes,** in what way? _____
7. Is your child suffering from any diabetes related complications? a)Yes b) No
   If **Yes**, which complications? _____
8. Has your child`s diabetes increased your responsibilities towards him/her?
   a) Yes b) No If **Yes** how? _____
9. Does having diabetes restrict your child from eating certain foods? a) Yes b) No
   If **Yes,** which foods? _____
10. Does your child sometimes eat the foods the doctor asked him/her not to eat?
    a) Yes b) No If **Yes**, why?_____
11. Does your child follow strictly the advice of the doctor on the kinds of food he/she is supposed to eat? a) Yes b. No If **No**, why? _____
12. Are there any other ways that having a chronic disease like diabetes affects the daily life of your child? _____
13. Is there anybody or child living with diabetes that your child admires? a) Yes b) No
14. How much does your child pay for transport from your house to the clinic or health centre? _____
15. Have you ever visited a herbalist because of your child`s diabetes? a) Yes b) No

Child/Adolescent Questionnaire

B. DIABETES KNOWLEDGE ASSESSMENT OF CHILD/ADOLESCENT: (Please tick the right answer) (ONLY FOR CHILDREN ABOVE 10 YEARS)

1. Which of the following is highest in carbohydrates?
   a. Chicken b. Fish c. Potato d. Beans
2. Which of the following is highest in fats?
   a. Milk b. Orange juice c. Maize d. Honey
3. Which is the best method for testing glucose?
   a. Urine testing b. Blood testing c. Both are equally good
4. What effect does unsweetened fruit juice have on your child's blood glucose?
   a. It lowers blood glucose b. It raises blood glucose c. It has no effect on blood glucose
5. What effect does exercise have on the level of blood glucose?
   a. It raises blood glucose b. It lowers blood glucose c. It has no effect on blood glucose
6. Having an infection is likely to cause which of the following?
   a. A decrease in the blood glucose b. An increase in the blood glucose c. No change in the blood glucose
7. Tingling and numbness may be symptoms of which of the following?
   a. Eye disease b. Nerve disease c. Kidney disease d. Liver disease
8. Which of the following is usually not associated with diabetes?
   a. Nerve problems b. Lung problems c. Eye problems d. Kidney problems
9. Signs of ketoacidosis (very high blood sugar) include?
   a. Shakiness b. Sweating c. Vomiting
10. If you are sick with the flu, which of the following changes should you make?
    a. Take less insulin b. Drink less liquids c. Eat more proteins d. Test for glucose more often

11. You realize just before lunch time that you forgot to take your insulin before breakfast. What should you do now?
    a. Skip lunch to lower your blood glucose
    b. Take the insulin that you usually take at breakfast
    c. Take twice as much insulin as you usually take at breakfast
    d. Check your blood glucose level to decide how much insulin to take
12. Low blood glucose may be caused by which of the following?
    a. Too little insulin b. Too much insulin c. Too much food d. Too little exercise
13. If you take your morning insulin but skip breakfast your blood glucose level will usually?
    a. Increase b. Decrease c. Remain the same
14. High blood glucose may be caused by?
    a. Not enough insulin
    b. Skipping meals
    c. Delaying your food
15. Glycosylated haemoglobin (haemoglobin A 1) is a test that is a measure of your average blood glucose level for the past:
    a. Day b. Week c. 3 months d. 6 months
16. What was your last HbA1c level? _____

10. STATEMENT ON PRE-RELEASE AND CONTRIBUTION

I, Loveline Niba, declare that the material in this thesis is original research carried out by me, parts of which have been submitted for publication in the journal *BMC Research Notes* and it is currently under peer review.

I was also responsible for the conception and design of the study, data collection and organization, statistical analysis, data interpretation and writing of the manuscript.

11. ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to the Center for International Health at Ludwig-Maximilians-Universität (CIH^{LMU}), Munich, Germany for the receipt of a scholarship to pursue a PhD program in Medical Research – International Health. This scholarship was funded by the German Academic Exchange Service (DAAD), the German Federal Ministry for Economic Cooperation and Development (BMZ) and Excellence Centers for Exchange and Development (EXCEED).

My profound gratitude goes to my LMU and local supervisors: Prof. Dr. med. Dr. h.c. Klaus G. Parhofer, Dr. med. Benedikt Aulinger and Prof. Wilfred F. Mbacham for their continuous support and substantial contribution towards the conception and design of this study, data collection, statistical analysis as well as data interpretation and drafting of the manuscript of this study. I wish to say I am indeed very grateful for all the guidance and advice throughout my study and more especially for the time and energy you all have spent in critically reading my manuscript.

My sincere gratitude also goes to the CIH team: Karsten Schacht, Andrea Kinigadner, Bettina Prueller, for offering me their support in various ways during the PhD program.

In addition, I am grateful to all the children from the diabetic clinics in the North West Region who participated in this study as well as the nurses in the two clinics who assisted in data collection.

Finally, I reserve special thanks to my husband, Kenneth and my parents for all the support and encouragement throughout my study.