DIABETES: A NEGLECTED DISEASE IN SUB-SAHARAN AFRICA

A comparative study between Rwanda and Norway.

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1. Summary

Aim: To illustrate diabetes care in Rwanda and to compare childhood diabetes care in Rwanda, Sub-Saharan Africa and Norway with guidelines from International Society for Pediatric and Adolescent Diabetes (ISPAD).

Methods: Part 1 and part 2: Literature review of diabetes care with focus on children with type 1 diabetes in Sub-Saharan Africa and Norway based on a non-systematic search on PubMed and on a standardized electronic questionnaire quality assessed with a local informant in Norway at Ullevål University Hospital (UUH). Part 3: A partly personal observational study from University Teaching Hospital (UTHB) in Rwanda based on eight pediatric case reports and an interview with a local informant.

Results: Norway has among the highest incidences in the world of type 1 diabetes in the age group 0-14 years (36 per 100 000 PYR), Rwanda has among the lowest (0.3 per 100 000 PYR). Type 1 diabetes constitutes the major subtype of diabetes among children and adolescents at UUH (92%) and UTHB (100%). The mean age at onset was 8.1 years at UUH and 10.2 years at UTHB. All children (100%) at UTHB had diabetic ketoacidosis at onset compared to 25 % at UUH. The most common administration form at UUH was continuous subcutaneous insulin infusion subsequently the pen and all subjects followed a multiple daily injection regime. At UTHB all patients used syringes and injections twice daily. Survival rate in Norway is 94.6% after 25 years. Type 1 diabetes in Rwanda reduces life expectancy with 20 years (from 58 years to 30 to 35 years). Having diabetes in a developing country as Rwanda implies a great financial burden on the family and outcome is often poor. Insulin availability remains a problem and urgent international financial support is needed. Re-hospitalized patients were admitted to hospital with multiple organ pathologies, but no registration of direct diabetic complications was done. Currently, there is no official diabetes registry or guidelines of diabetes care in Rwanda.

Conclusion: Diabetes is still a neglected disease in Rwanda, though, greater awareness and knowledge is rising. Implementing of current ISPAD guidelines is not possible in Rwanda emphasizing the importance of new guidelines directed towards developing countries.

2. Abbreviations

ACR	Albumin Creatinine Ratio
ADA	American Diabetes Association
AER	Albumin Excretion Rate
AIDS	Acquired Immunodeficiency Syndrome
BG	Blood Glucose
CMR	Child Mortality Rate
ECG	Electrocardiogram
EDIC	Epidemiology of Diabetes Interventions and Complications study
EUR	Euro
DCCT	The Diabetes Control and Complications Trial
DERI	Diabetes Epidemiology Research International study
DIAMOND	Diabetes Mondiale Study
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DN	Diabetic Nephropathy
DR	Diabetic Retinopathy
EDIC	Epidemiology of Diabetes Interactions and Complications study
ESRD	End Stage Renal Disease
EURODIAB	Europe and Diabetes study
GDP	Gross Domestic Product
GFR	Glomerular Filtration Rate
FPG	Fasting Plasma Glucose
HbA1c	Hemoglobin A 1 C
HIV	Human Immunodeficiency Virus
IDDM	Insulin-Dependent Diabetes Mellitus
IDF	International Diabetes Federation
IGT	Impaired Glucose Tolerance
IFG	Impaired Fasting Glucose
IHD	Ischemic Heart Disease
ISPAD	International Society of Pediatric and Adolescence Diabetes
JVP	Jugular Vein Pressure
MDI	Multiple Daily Injections
MODY	Maturity Onset Diabetes of the Young
MRDM	Malnutrition-related Diabetes Mellitus
NCDR	Norwegian Childhood Diabetes Registry
NIDDM	Non-Insulin-Dependent Diabetes Mellitus
NPH	Neutral Protamine Hagedorn
OGTT	Oral Glucose Tolerance Test
OPC	Outpatient Clinic
PDR	Proliferative Diabetic Retinopathy
p-glu	Plasma Glucose
PYR	Patient-Years
RwF	Rwandese Franc
s.c	Subcutaneous
SSA	Sub-Saharan Africa
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TSH	Thyroid Stimulating Hormone
UUH	Ullevål University Hospital
UKPDS	United Kingdom Prospective Diabetes study
UTHB	University Teaching Hospital of Butare
WHO	World Health Organization

3. Introduction

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1,2]. Diabetes has been recognized since antiquity and its symptoms, which include excessive drinking and frequent urination, were noted on Egyptian papyrus in about 1550 BC (later recognized by George Ebers) [3]. The role of the pancreas in diabetes was described in 1889 by Joseph von Mering and Oscar Minkowski [4], eventually leading to the discovery of insulin in 1921 by Sir Frederick Grant Banting and Charles Herbert Best [5]; this changed the outcome of diabetes dramatically. Before the discovery of insulin, patients with type 1 diabetes (T1D) became emaciated and usually died within one or two years after diagnosis [6]. The first patient was treated in 1922 and The New York Times declared that insulin could cure diabetes [7]. Mortality rates in patients younger than 20 years declined dramatically a few years later [6]. However, with the introduction of insulin patients lived longer and complications became more apparent. Renal failure, cardiac arrest, blindness, gangrene and other complications typically shortened life expectancy by 15 years [8].

Until the 1950s physicians did not distinguish between T1D and type 2 diabetes (T2D). Still, they recognized a difference between what they called "acute" and "chronic" [7]. Insulin had a more dramatic effect on individuals with the "acute" form, which affected primarily young children. The "chronic" form tended to affect the middle-age, elderly obese and this form was insensitive to insulin. Currently, the "acute" form represents T1D and the "chronic" form represents T2D. In 1999, the World Health Organization (WHO) suggested a subdivision into four main groups of diabetes; T1D, T2D, gestational diabetes and other specific types (heterogenic group) [9], the latter includes diabetes caused by: genetic defects in beta-cell function, frequently called "Maturity Onset of the Young" (MODY), genetic defects in insulin action, genetic syndromes associated with diabetes and diabetes secondary to other conditions, such as pancreatitis and cystic fibrosis.

Despite increased availability of insulin, worldwide mortality is not declining and both prevalence and incidence appears to be increasing. Mortality is an important measure of population health and is often used to assign priorities in health interventions. The International Diabetes Federation (IDF) estimated that four million deaths in the 20-79 age group may be attributable to diabetes in 2010, accounting for almost 7% of global mortality, equal to many infectious diseases like Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) [10,11]. Deaths attributable to diabetes in a global perspective have been challenging to estimate because one third of the countries of the world do not have reliable data. Most of these are countries in Sub-Saharan Africa (SSA) [10]. Routinely reported statistics based on death certificates can underestimate mortality by threefold because individuals often die of cardiovascular and renal disease and not from a cause uniquely related to diabetes [12]. Diabetes is increasing most rapidly in developing countries, where industrialization and

urbanization have led to the adoption of a western lifestyle. According to WHO around 220 million people had diabetes in 2011 and the rate is predicted to double by 2030 [13].

4. Aims

The aim of this thesis is to illustrate diabetes care in Rwanda and to compare childhood diabetes care in Sub-Saharan Africa and Norway according to guidelines from International Society for Pediatric and Adolescent Diabetes (ISPAD). All forms of diabetes will be discussed, however, the main focus of the thesis will be on pediatric T1D. Relatively few studies on diabetes have been done in SSA earlier and I hope this study can contribute to an increase in the knowledge and awareness of diabetes in SSA.

Additionally, this thesis is part of a larger study called "Diabetes in children; a global comparative study". Medical students in this project go to various countries in the world to observe and study diabetes care based on a standardized questionnaire.

5. Methods

This thesis is based on a literature review of diabetes care in SSA and Norway. Included is an observational study about Rwanda, based on eight pediatric case reports from a university hospital in Rwanda.

A non-systematic search on PubMed was performed to find published literature on diabetes in SSA and Norway. Data from Norway was additionally provided by the Norwegian Childhood Diabetes Registry (NCDR) and a local informant, diabetic nurse Siv Janne Kummernes at Ullevål University Hospital (UUH) in Oslo. I observed outpatient clinic (OPC) consultations at UUH together with paediatrician and endocrinologist Dr. Torild Skrivarhaug. Eight case reports were retrieved from University Teaching Hospital of Butare (UTHB) to gather information on diabetes care in Rwanda in addition to my personal experience from spending seven weeks at this hospital (five weeks at paediatrics and two weeks at internal medicine) and an interview with a paediatrician at this hospital, Professor JWO Iraka.

We designed a standardized electronic questionnaire (appendix 1) largely based on international guidelines posted by ISPAD and American Diabetes Association (ADA). The questionnaire was divided into two parts. The first part was designed to map diabetes in children at a national or regional level. This part included figures on: incidence, prevalence, mortality, complications, patient organizations, demographics and economy. The first part of the questionnaire was based on information available on the internet and other available sources. The information was then quality assessed with the local informant. The second part was designed to map how children with diabetes are followed up at the local hospital/treatment centre. The interview contained multiple open, qualitative questions.

6. PART 1: Literature review

6.1. Type 1 Diabetes

Epidemiology for type 1 diabetes

T1D is the most common endocrine and metabolic disease in childhood. In 2010, the total child population of the world (0–14 years) was estimated to be 1.9 billion, of whom 0.02% have diabetes [9]. This means that approximately 480,000 children around the world have diabetes with 76,000 new cases diagnosed each year reflecting an annual incidence increase of 3% [9]. Two international collaborative projects, the Diabetes Mondiale study (DIAMOND) [14] and the Europe and Diabetes study (EURODIAB) [15] have monitored trends in incidence. There is a worldwide increase in both low incidence countries and high incidence countries, with the strongest increase in the former [9]. Studies are contradictory with the overall increased incidence is a result of clinical manifestation at a younger age, rather than a worldwide increase in the lifetime number of patients with the disease [16-21]. Especially in African countries it is difficult to conclude as long as child mortality is high and it is likely that many children die before clinical manifestations of diabetes can be monitored.

T1D is diagnosed in all age groups with a peak incidence around puberty (10-14 years) [14], the incidence increases progressively with age towards this peak. In a study from Sweden [20] the peak appeared in a younger age group (5-9 years old), this support the observation that diabetes is more frequently diagnosed in younger age groups [18-21]. T1D incidence in the age group 0-14 years varies greatly between countries, within countries and between different ethnic populations [14]. Finland has the highest incidence rate of 57.6 per 100 000 patient-years (PYR) [1,22] and China and Japan has the lowest with 0.1 and 2.4 per 100 000 PYR [23,24]. Norway is a high incidence country with 36 per 100 000 PYR [25], unfortunately data for Rwanda is not available.

There is an enormous (30-fold) international variation in the frequency of the T1D. This difference also accounts for variation in mortality rate between developed and developing countries, but also between developed countries as well [26-28]. Figures from the Diabetes Epidemiology Research International study (DERI) [26,27] demonstrates that individuals with T1D in Sofia, Bulgaria, were ten times more likely to die than those in Norway prior to the age of 25 years. In developed countries patients with T1D have a two to tenfold increased risk of dying compared to baseline populations. In developing countries some patients die within a few years [28].

Etiology and pathogenesis for type 1 diabetes

T1D is characterized by selective destruction of the insulin producing pancreatic islet β-cells, usually leading to absolute insulin deficiency; the etiology is not completely understood. Serological markers as islet cell antibodies, glutamic acid decarboxylation, islet antigen 2, islet antigen 2 beta and insulin autoantibodies of an autoimmune pathological process, are present in 85-90% of individuals when

fasting hyperglycemia is detected [29,30]. Susceptibility is determined by multiple genes and haplotypes [31,32]. Although family aggregation accounts for approximately 10 % of cases of T1D, there is no recognizable pattern of inheritance [33]. Environmental triggers which initiate and drive beta cell destruction still remain largely unknown [34].

The clinical presentations of T1D vary according to the rate of beta cell destruction. In general, the rate is rapid in infants and children and slower in adults and the presenting symptoms vary accordingly. The classic history of new onset T1D includes increasing polyuria, polydipsia, excessive thirst and weight loss over two to six weeks; especially in young patients the first manifestation can be ketoacidosis [1,35].

Symptoms usually appear when more than 90 % of the β-cells have been destroyed [36]. As insulin is the mediator for glucose uptake into the cells, lack of insulin will gradually lead to hyperglycemia and diabetic ketoacidosis (DKA). Increased blood glucose (BG) can be asymptomatic but as the hyperglycemia progresses it will exceed the renal threshold (10mmol/l) and result in: osmotic diuresis, dehydration, loss of electrolytes and vomiting leading to induced release of stress hormones. Stress hormones, glucagon, cortisol and growth hormone will increase insulin resistance and further aggravate the hyperglycemia, hyperketonemia and hyperosmolality. Hyperketonemia evolves as the tissues metabolize fatty acids instead of glucose and ketones accumulate in the blood producing ketosis, ultimately leading to coma and death.

Diabetic ketoacidosis

Clinical manifestations of DKA are: dehydration, rapid and deep sighing (Kussmaul respiration), nausea, vomiting, abdominal pain mimicking an acute abdomen, progressive obtundation and loss of consciousness, increased leukocyte count with left shift, non-specific elevation of serum amylase and fever when infection is present [37]. Biochemical criteria for diagnosis of DKA according to ISPAD are [38]:

- Hyperglycemia (BG >11 mmol/L [≈200 mg/dL]).
- Venous pH <7.3 or bicarbonate <15 mmol/L.
- Ketonemia and ketonuria.

6.2. Type 2 Diabetes

Epidemiology for type 2 diabetes

In most western countries T1D accounts for more than 90 % of the cases among children and adolescents, while T2D affects predominantly the elderly [20,39]. In contrast, the incidence of T2D in young onset diabetes is nearly 50% in Taiwan [40] and more than 90 % in Hong Kong [41]. In

contrast to T1D, T2D is associated with a strong family history of diabetes (80% having parents with DM) [1].

Not all patients present as a classic T2D picture in overweight and obese patients. One third of the patients with T2D present a picture of DKA [42], which is often misdiagnosed as T1D. The diagnosed autoimmune "T2D" is most likely autoimmune T1D in overweight and obese individuals with underlying insulin resistance (15 to 40% have T1D-associated auto-antibodies) [43]. Hemoglobin A 1 c (HbA1c) concentrations are significant higher in these individuals, β-cell function is significantly less and they require insulin treatment sooner. Diabetes autoantibody testing should be considered in all pediatric patients with the clinical diagnosis of T2D, because of the high frequency of islet cell autoimmunity in otherwise ''typical'' T2D, as antibodies will indicate an earlier need for insulin [43].

Etiology and pathogenesis for type 2 diabetes

T2D is characterized by insulin resistance in peripheral tissues, but may range from predominantly insulin resistance with relative insulin deficiency, to a predominantly secretory defect with or without insulin deficiency. Insulin resistance is an impaired response to the physiologic effects of insulin, and diabetes is only one of the manifestations of the insulin resistance syndrome commonly associated with T2D. Other manifestations of this syndrome include obesity, nephropathy, hypertension, dyslipidemia, ovarian hyperandrogenism and non-alcoholic fatty liver disease [43,44].

Treatment for type 2 diabetes

The treatment for T2D is given according to the severity of the situation determined by symptoms, hyperglycemia and presence or absence of ketosis. Asymptomatic children can be treated non-pharmaceutical but if normalized fasting BG is not achieved with dietary modifications and lifestyle changes, pharmacotherapy will be necessary. Initial pharmaceutical treatment involves oral tablets designed to increase insulin sensibility, suppress hepatic glucose production, enhance peripheral glucose uptake, increases fatty acid oxidation, and decreases absorption of glucose from the gastrointestinal tract. The final stage in T2D treatment is insulin therapy as for T1D patients.

6.3. Diagnostic criteria

Different sets of diagnostic criteria for diabetes mellitus have been reported by WHO/IDF (2006) [45] and ISPAD (2009) [1]. In both sets the criteria applies for T1D, T2D and other specific types. ISPAD recommendations are directed especially towards children and adolescents; based upon the WHO report from 1999 [35] and guidelines from ADA [2]. According to ISPAD the diagnosis of diabetes is based on BG measurements and/or presence of symptoms [1]:

1. Fasting plasma glucose (FPG) ≥ 7.0 mmol/l (126 g/dl). Fasting is defined as no caloric intake for at least 8 hours.*

2. Plasma glucose (p-glu) two hours after oral glucose tolerance test (OGTT) ≥ 11,1mmol/l (200g/dl). The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
3. Symptoms of hyperglycemia and a casual plasma glucose concentration ≥ 11,1mmol/l. Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.

*In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.

The clinical diagnosis of T2D in an asymptomatic individual requires at least two abnormal glucose values, diagnostic of diabetes on two separate days, or the same criteria as for T1D [1,43].

In individuals that don't fulfil the diagnostic criteria for diabetes, but still present a abnormal picture, impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are measured. IGT and IFG are intermediate stages between normal glucose homeostasis and diabetes. IGT is defined as two hour post-load glucose between 7.8-11.1mmol/L. IFG is defined as fasting glucose between 5.6-6.9mmol/L. IGT and IFG are now referred to as pre-diabetes indicating high risk of developing diabetes. These individuals should be tested with an OGTT.

6.4. Treatment

The treatment for T1D and insulin dependent T2D is lifelong insulin substitution. Insulin therapy has changed dramatically since the first patient was treated in 1922. In the earliest years insulin therapy usually consisted of one injection before each meal and one at 1 a.m. When intermediate and long-acting insulin became available in 1935, most patients moved to one or two injections per day. In the 1960s it became obvious that those using multiple daily injections (MDI) (≥ four injections per day) developed retinal complications less frequently than those on one or two injections a day (9 % vs. 61 %) [46]. Today, guidelines recommend four or more injections per day.

In the resent years new insulins and new devices for administration has led to improvement in the care of diabetes, but the extent in a clinical long term setting has not been elucidated [47]. Different types of insulin are available worldwide; human insulins, porcine and bovine insulins and the newer analogs. In children and adolescents no significant improvement in BG control was observed with insulin analogs compared to regular insulin, but, however, a reduction in hypoglycaemic episodes has been observed among adolescents [48,49]. It has not been demonstrated that human insulins are more efficient than porcine and bovine, though the latter has been associated with greater immunogenicity [50]. Porcine and bovine insulin may be more economical and more readily available in some parts of the world. However, animal species insulins are being withdrawn from the market by the

pharmaceutical companies. The major manufacturers are moving towards production of analogs only [47], which are 50-100% more expensive than the traditional insulin [51].

According to ISPAD, children and adolescents should at least have access to adequate amounts of regular insulin and intermediate acting, Neutral Protamine Hagedorn (NPH) insulin [47]. In most parts of the world regular insulin is still used as an essential component of most daily replacement regimes. The advantages with the rapid acting analogs are that they can, when needed, be given immediately before meals, or after food intake. Basal insulin analogs are superior to traditional long acting insulins and it has also been demonstrated that they produce a more predictable insulin effect with less day to day variation compared to NPH insulin [52].

Principals of insulin therapy

The three frequently used regimes are described in ISPAD guidelines: two and three injections daily and the basal bolus regime [47].

1. *Two injections daily* with a combination of rapid analogs/regular insulin and intermediate acting insulin (before breakfast and the main evening meal). Two thirds of the dose should be given in the morning and one third in the evening. One third should be short acting and two thirds intermediate acting.
2. In the regime with *three injections daily,* insulin is administrated before breakfast; rapid analogs/regular insulin and intermediate, before afternoon snack; rapid/regular insulin and before bed; intermediate.
3. The *basal bolus regimen* require injection of intermediate or basal insulin/long acting analog at bedtime or twice daily in addition to injection of rapid analogs/regular insulin before each meal. 40-60% should be basal long acting insulin, the rest pre-prandial rapid analogs/regular insulin. 30-50% of intermediate acting should be given at night time.

Daily insulin dosage depends on factors such as age, weight, duration of diabetes, nutritional intake and exercise. Optimal dosage should be the dose that best achieves glycemic control. ISPAD guidelines suggest [47]: During partial remission phase, sufficient total daily insulin dosage is often <0.5 IU/kg/day. Pre-pubertal children (outside partial remission phase) usually require 0.7-1.0 IU/kg/day. During puberty, requirements may rise to above 1 and even up to 2 IU/kg/day.

Administration forms

Currently, the basal bolus-regime is the best way to imitate the physiological insulin profile [47]. Continuous subcutaneous insulin infusion (frequently called insulin pump therapy) is often used with this regime. Insulin is infused subcutaneously (s.c) at a pre-programmed basal rate and the patients add bolus doses to the balance intake of carbohydrates. New modalities such as pumps, pens, subcutaneous

indwelling catheters and automatic jet devices are more expensive than the conventional syringes and implementation is not possible in many countries [47].

6.5. Treatment target

The established treatment target is to maintain the BG concentration as close as possible to normal range (3.6-5.8mmol/L). To obtain this, intensive insulin treatment, self-monitoring of BG and regular measures of HbA1c is necessary. HbA1c is a form of hemoglobin which is measured primarily to identify the average plasma glucose levels for the preceding four to twelve weeks [53] and this serves as a marker for long term BG levels but it does not take into account fluctuations, which may play a role in development of complications [54].

ISPAD practical recommendations are based on findings in Diabetes Control and Complications Trial (DCCT) [55-57] and United Kingdom Prospective Diabetes Study (UKPDS) [58]. DCCT was a major clinical study conducted from 1983-93 and involved 1,441 volunteers with T1D, ages 13 to 39, in United States and Canada. UKPDS was a randomized trial involving 5,102 patients with newly diagnosed T2D that ran for 20 years (1977 to 1997) in the United Kingdom. DCCT demonstrated that intensive diabetes treatment both delays the onset and slows the progression diabetic complications in T1D subjects and related lower Hb1Ac values to less complications [56]. The mean HbA1c value after three months was 2% lower (7.2% vs. 9.1%) in the intensive treated group compared to the conventional group (injections twice daily). In UKPDS each 1% reduction in updated mean HbA1c was associated with a 21 %, risk reduction of diabetes related death, 14 % risk reduction for myocardial infarction and 37 % risk reduction of microvascular complications.

ISPAD treatment goals [59] for children with diabetes up to 18 years is HbA1c value less than 7.5% and for adults is HbA1c less than 7.0%, both with repeated monitoring every three months. Current glycemic targets for patients with diabetes make no distinction as to the type of diabetes.

6.6. Complications

Chronic hyperglycemia is associated with damage to small and large vessels, mainly affecting the cardiovascular system, the kidneys, the retina and the peripheral nervous system. The Epidemiology of Diabetes Interventions and Complications Study (EDIC) was a follow up study of the DCCT, eight years after intervention. EDIC [60,61] confirmed the risk reduction for microvascular complications and provided evidence that intensive diabetes treatment and improved glycemic control lead to a significant risk reduction for macrovascular complications compared to conventional treatment.

Clinically evident complications are rare in childhood and adolescence T1D, however, abnormalities may be present a few years after onset of the disease. On the contrary, clinical presentation of T2D is often slow progressing and manifested complications such as dyslipidemia, hypertension and

albuminuria may be present at diagnosis and should be assessed after blood glucose control has been optimized [43]. In addition, complication testing at diagnosis should include eye examination, liver enzymes and control for obstructive sleep apnoea. Risk factors for the development of complications are longer duration of diabetes, older age, puberty, smoking, hypertension and family history of complications [62,63].

In general, areas with specialized centres report a declining incidence of complications [63] and areas where health care is not optimal hold a greater risk of complications [64]. However, this does not undermine the importance of good glycemic control.

Microvascular complications

Microvascular complications include retinopathy, nephropathy and neuropathy and they are associated with a high degree of morbidity and mortality.

Diabetic retinopathy

In developed countries diabetic eye disease is among the leading cause of blindness and it is the fifth leading cause of global blindness, affecting an estimated 1.8 billion people [65]. Diabetic retinopathy (DR) causes microvascular retinal changes and may lead to visual impairment and blindness. After 20 years of diabetes nearly all patients with T1D have some degree of DR [66]. Adolescents have a higher risk of progression to vision threatening retinopathy compared with adults [62].

Diabetic nephropathy

Diabetic nephropathy (DN) is a major cause of morbidity and mortality among young adults with T1D. DN is characterized by progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli. It is defined as persistent proteinuria (greater than 500 mg/24 hours) or albuminuria (greater than 300 mg/24 hours) [62]. The first clinical sign of progression to DN is microalbuminuria. Microalbuminuria is defined in one of three ways [62]:

- Albumin concentration 30–300 mg/L
- Albumin excretion rate (AER) between 20 and 200µg/min or AER 30–300 mg/24 hours in 24-hours urine collections
- Albumin creatinine ratio (ACR) 2.5–25mg/mmol or 30–300 mg/gm (spot urine)

Persistent microalbuminuria and DN is associated with decreased glomerular filtration rate (GFR) and indicates progression to end stage renal disease (ESRD). ESRD is the prime indication for dialysis and kidney transplantation in many Western countries. DN accounts for 25 to 30% of the patients with ESRD who require dialysis and it has been estimated that 30 to 40% of patients with IDDM will eventually develop ESRD [56,67]. The process can be slowed by intensive treatment as shown in EDIC [60]. Only 6.8% of the participants in the previous intensive-treatment group developed microalbuminuria and 1.4% developed clinical albuminuria, compared with 15.8% and 9.4% of

participants in the previous conventional treated group. The total number of severe kidney events (kidney insufficiency) was more than three times greater in the conventional treated group.

Diabetic neuropathy

Diabetic neuropathies are a heterogeneous group of disorders which can affect both the somatic and autonomic nervous system. Diabetic sensorimotoric polyneuropathy is the most common form and is often referred to as "diabetic neuropathy". Neuropathy can cause morbidity with significant impact on the quality of life of the person with diabetes, and can result in early death. The major morbidity is foot ulceration, which can lead to gangrene and ultimately to limb loss. Diabetic neuropathy is the most common form of neuropathy in developed countries and is responsible for 50 to 75% of non-traumatic amputations [68]. A population survey [69] reported that 30% of IDDM and 36 to 40% of non-insulin-dependent diabetes mellitus (NIDDM) patients with diabetes experienced neuropathic symptoms. It is expected that diabetic neuropathy is grossly underdiagnosed and undertreated in many countries. Management of the disease is complex and the key to success depends, in part, on discovering the underlying pathological processes in each particular clinical presentation. There has been an increase in the understanding of the pathogenesis of diabetic neuropathies over the last decades and new therapies are emerging that hold promise for the treatment [68].

Macrovascular complications

Macrovascular complications include heart disease, stroke and peripheral vascular disease (which can lead to ulcers, gangrene and amputation). Cardiovascular complications constitute the major cause of mortality in patients with T1D and T2D and life expectancy in T2D patients, diagnosed prior to the age of 40 years, is reduced by eight years relative to people without diabetes [70]. Epidemiological studies have demonstrated that diabetes is an independent risk factor for cardiovascular disease and is associated with a two- to fourfold increased risk of coronary heart disease [71,72].

Type 1 diabetes

EDIC reported that cardiovascular benefit was observed ten years after intensive treatment [61]; a 42% decrease in the cardiovascular event rate and a 15 to 33% reduction in myocardial infarction in T1D subjects [57].

Type 2 diabetes

It is evident that early intensive glycemic control seems to reduce the risk of cardiovascular event later in life. In the last two years several trials among T2D patients [73-75] have investigated if even more intensive glycemic control (HbA1c 6.4-6.9% compared to HbA1c 7.0-8.4%) results in a further reduction in cardiovascular disease and mortality. Intensive control did not seem to influence the outcome in short term (3 to 6 years after) when initiated in those diagnosed many years previously. In one study [74], mortality did increase in the intensive treated group and because of the many hypoglycaemic episodes, this study was stopped after 3.5 years. It remains unclear if it was the high

rate of hypoglycaemic episodes that was the cause of increased mortality. One suggestion was that less strict HbA1c goals than 7.0% might be indicated for patients who had extensive co-morbid conditions, limited life expectancy, or an increased risk of severe hypoglycemia [76].

7. PART 2: Diabetes in a global perspective with focus on sub-Saharan Africa and Norway.

In general, data on the impact of diabetes in SSA countries is limited often outdated and full texts are not always available electronically. In 2009, the IDF African Region launched its action plan [77] to tackle the escalating threat from diabetes. At the same time, ISPAD proclaimed that the new practical recommendations had to be applicable for the total diabetes community worldwide [1]. With this in mind, it is important to remember that each Sub-Saharan African country is unique.

Many publications from this region originate from South Africa which is not considered representative for the entire region. South Africa is ranked higher (number 110) than most SSA countries on UNs Global Human Development Report [78]. The report is based on: life expectancy, Gross Domestic Product (GDP) per capita, literacy rate, inequality (disproportionate distribution of income, medical services and access to education), the index of gender equality and poverty. Rwanda is ranked number 152 out of 169 countries and Norway is ranked as number one [78]. It is reasonable to assume that countries where it is possible to retrieve data on diabetes care are more developed than the ones where data does not exist at all.

7.1. PART 2A: Diabetes in Sub-Saharan Africa

7.1.1. Chronic diseases in a global perspective

The health landscape of SSA is dominated by poverty and a high burden of infectious diseases, including HIV/AIDS and malaria. Many African countries now face a double disease burden, with increasing numbers of patients with non-communicable diseases such as: hypertension, stroke, coronary heart disease and diabetes. Over the last 25 years diabetes has become a major health problem in developing countries. While there has been a great improvement in the knowledge, epidemiology and management of diabetes in the developed world, there has been little or no improvement in SSA. Professor Jean Claude Mbanya from Cameroon was elected as the first African President of IDF from 2009-2012; a sign of new international attention on diabetes in Africa.

The T2D epidemic seen in the developed world the last years appears to have reached SSA as well. Currently, the population of SSA is predominantly rural (34% urban), but by 2025, more than 70% of the population will live in the urban areas [79]. T2D is increasing most quickly in developing

countries where: rapid uncontrolled urbanization and major changes in lifestyle towards western diets, increased food quantity with reduced quality, low levels of exercise, smoking and increased alcohol availability as well as increased life expectancy could be driving this epidemic. With the obesity problem on one side, it is a well-known phenomenon that malnourishment malnutrition and stunted growth in children leads to increased risk of obesity and insulin resistance later in life, predisposing to T2D [80,81]. To aggravate the situation further, antiretroviral drugs are widely being used in African patients with AIDS, with the metabolic syndrome and T2D as common adverse effects [82].

It is likely that children with T1D in SSA often go undiagnosed, or if diagnosed do not have access to insulin, and die as a result. The outcome from diabetes in some developing countries is similar to outcome before the discovery of insulin. In 1980, it was announced that life expectancy of a child with newly diagnosed T1D in Tanzania might be as short as one year (20 % died within the first year) [83]. Today, the situation appears to have improved in some areas, however, this is not true for all regions. IDF Africa published in 2006 an article stating that life expectancy of newly diagnosed children with T1D in some countries still could be less than seven months [84]. Unfortunately, studies to confirm or disprove this statement are limited.

7.1.2. Epidemiology in sub-Saharan Africa

The estimated prevalence of DM in Africa is 1% in rural areas, up to 5% to 7% in urban SSA and between 8% and 13% in more developed areas such as South Africa [85-87]. Although the majority of patients, 70% to 90%, present with typical T2D, up to 25% are considered to have T1D [88-90]. Among the latter group, it is currently estimated that approximately 15% [91] may represent atypical presentations of diabetes, especially ketosis-prone atypical diabetes and malnutrition-related diabetes mellitus (MRDM). The nature and existence of both these subtypes is still uncertain [82] and there is no reliable data. Findings suggest that the characteristics of T1D in people from SSA can differ somewhat from typical European populations. One interesting feature of African T1D is that the age of onset is about ten years later than elsewhere. In South Africa mean age at presentation was 22-23 years African T1D patients [92]. In Tanzania [93] and Ethiopia [94] similar observations were made; the peak age at presentation was 15 to 19 years and 20 to 25 years respectively. Half of African American patients initially treated with insulin do not have classical T1D [95] and may explain the difficulty in classifying and diagnosing some forms of diabetes in Africa.

Ketosis-prone atypical diabetes mellitus

Ketosis-prone atypical diabetes mellitus affects people with a T2D phenotype and profile, but the initial clinical presentation mimics T1D and presents with severe hyperglycemia and ketosis [43,96]. Within days or weeks after initial insulin treatment, long-term remission with or without relapses is achieved by low-dose oral hypoglycaemic drugs, lifestyle intervention, or both [96].

Malnutrition-related diabetes mellitus

MRDM or "Tropical diabetes" was described in the 1960s and 70s and is a rare type of diabetes associated with long term malnutrition [97]. It is characterised by insulinopenia, insulin resistance, hyperglycemia and failure of the beta-cells in the pancreas, often seen as calcifications. These patients are thin, young (below the age of 30 years) and severely hyperglycemic. However, in contrast to T1D, these patients do not have ketonuria, do not develop ketosis and they require very high doses of insulin for glycemic control [98].

Prevalence and incidence

In the IDF Diabetes Atlas report from 2010 (based on DIAMOND) that only four SSA countries contributed with data on prevalence and incidence in childhood diabetes [99]. Prevalence of T1D is low compared to Western countries (table 1); 0.33 per 1000 in Nigerian schoolchildren [100] and 0.95 per 1000 in Sudanese schoolchildren [101]. Incidence rates of 10 per 100,000 PYR have been reported from Sudan [102] and 1.5 per 100,000 PYR from Tanzania [103]. Kengne et al. [104] refer estimates of the total number of patients with T1D and T2D in several SSA countries based on the IDF Diabetes Atlas 2000 and the World Bank (table 2). IDT estimate the current overall T2D prevalence on the African continent to be 2.4% [105] (compared to 7% in Norway).

Table 1: Figures on prevalence and incidence of T1D in children and adolescents in Sub-Saharan Africa. *IDDM=Insulin Dependent Diabetes Mellitus.PYR= patient-years.

Country	Year	Authors	Age (years)	Prevalence (per 1000)	Incidence (per 100 000 PYR)
Nigeria	1992	Afoke et al. [100]	5-17	0,33	
Sudan	1989	Elamin et al. [101]	7-14	0,95*	
Sudan	1992	Elamin et al. [102]	< 15		10,1
Sudan	1991-1995	Elamin et al.[106]	< 15		10,3
Tanzania	1982-1991	Swai et al.[103]	0-19		1,5

Table 2: Figures on total number of patients diagnosed with type 1 and type 2 diabetes in Sub-Saharan Africa countries (based on the IDF Diabetes Atlas 2000 and the World Bank) [104].

Country	Total number of people with diabetes (x1000)	
	Type 1 diabetes	Type 2 diabetes
Ethiopia	4.95	268
Nigeria	12.52	209
South Africa	57.56	886
Tanzania	2.47	134.8
Democratic Republic of Congo	4.8	252.6

7.1.3. Mortality in Sub-Saharan Africa

More than 330,000 people are expected to die from diabetes-related causes in the Africa region, accounting for 6% of all deaths in the 20-79 age groups in 2010 [12]. In contrast, diabetes accounts for 15.7% of deaths in North America [12].

There is only one longitudinal study on mortality in T1D patients from SSA conducted in South Africa from 1982-2002 (mean age 22 years, mean duration 3 years) [89]. Mortality after 20 years was 43% (excluding the 40% who were lost to follow-up for unknown reasons). Renal failure as a result of DN was the main cause of death (43%) followed by metabolic, particularly hypoglycemia (29%), DKA (10%) and infection (10%). Older studies from Sudan [107] and Tanzania [108] reported five year mortality rates of 20% (T1D) and 29% (mainly IDDM) respectively. If patients lost to follow-up were included, five year mortality rates would reach 50% and 40%. For T2D patients in Tanzania the five year mortality rate was 16% [108]. Despite a lack of studies of patients younger than 20 years, there are relatively few deaths in this group and this will, therefore, not be affecting the conclusions made. Though, misdiagnosis or delayed diagnosis may contribute to false low mortality rate, especially in the children less than five years old.

7.1.4. Complications in Sub-Saharan Africa

Acute complications

The acute metabolic complications of DKA, hyperosmolar non-ketotic coma and hypoglycemia all commonly occur in Africa and have a worse prognosis than in developed countries. Most children (75-80%) present with DKA at the time of diagnosis [94,107,109]. Up to 90% of children and adolescents with T1D [107,109] reported one or more episodes of DKA over the last six months, other studies report a variation from 25-90% [94,107]. Mortality rate of DKA is 10-30% [105] and 41% in hyperosmolar non-ketotic coma patients [110]. Severe hypoglycemia with unconsciousness and/or convulsions occurs in 25-55% (last six months period) [94,109].

Chronic complications

Populations of African origin have a high prevalence of microvascular complications of diabetes, with renal failure (secondary to DN) as the leading cause of death in this group of patients [89]. Most studies on diabetic complications in SSA are based on findings in adults and/or do not separate T1D and T2D. Current data was difficult to find, the most recent study of complications was from Malawi from 2011 [111,112]. It separated T1D and T2D regarding DR but not DN or neuropathy. In a review from 2009 [82] references were often more than ten years old.

Diabetic retinopathy

One study from Dar es Salaam, Tanzania [109] (from 2005-6) involving T1D children and adolescents reported that 22.2% had DR (5-18 yrs of age, mean diabetes duration 5 yrs). Two longitudinal cohorts included T1D patients, one from South Africa [89] and one from Malawi (T1D and T2D) [111]. In South Africa, 59% of T1D subjects developed DR after mean duration 23 years. In Malawi, prevalence of DR was 28.1% after mean diabetes duration 6.7 years, of whom 12.5% had PDR. In T2D patients with duration longer than five years, prevalence of DR was 23.2% and PDR or worse was 3.2%. In those with disease duration longer than 16 years, prevalence of DR was 66.7% and proliferative diabetes retinopathy (PDR) and blindness were 14.3%. These findings are similar to earlier reports (10-15 years old) where overall retinopathy prevalence in (mainly) adult T2D patients varied from 15-56% [88,113-115] depending on the duration of diabetes and glycemic control.

Diabetic nephropathy

In a 20 year follow-up cohort from South Africa [89], chronic renal failure (secondary to DN) was responsible for up to 50% of all-cause mortality in T1D patients and 1/3 to 1/2 of people in dialysis had diabetes. After a mean duration of T1D of 23 years 35 % had [89]. DN was reported in 22% of Sudanese patients with IDDM (mean duration 10 years) [116]. In Ethiopian adult IDDM patients (older than 18 years) [117] it was found that the prevalence of albuminuria increased from 25% in those with a duration less than two years to 80% in those with diabetes duration of ten years or more. Microalbuminuria was present in 32% of IDDM patients (mean diabetes duration 6 years) [117]. Microalbuminuria was present in 29.3 % of children and adolescents from Tanzania with T1D [109], increasing prevalence with older age. Neither of these studies report of pharmaceutical intervention.

Nephropathy has been reported in 34.7% of Malawian (mainly T2D patients, mean diabetes duration 7 years) [112]. In Nigeria, nephropathy was reported in 41.1% of T2D patients (mean diabetes duration 12 years) [118].

Diabetic neuropathy

In Sudanese IDDM patients neuropathy was found in 27% (diabetes duration 6 to 10 years) and in 76% (duration longer than 10 years) [116]. In Ethiopia [119] and South Africa [120] prevalence of neuropathy in IDDM patients was respectively 7.9% (mean diabetes duration 15 years) and 42% (mean diabetes duration 13.6 years); all data are from 1992-95. In South Africa the prevalence of neuropathy was 27.6% after eight years diabetes duration (mainly NIDDM). Neuropathy in newly diagnosed Ugandan patients was found in 46.5% of patients (mean age 45 years) [121]; no distinction was made between T1D and T2D.

Diabetes neuropathy was the most common cause (80%) [122] of foot ulcer and the outcome was often amputation, 33% in one study [123]. Foot ulcers were found in 15% of all adult diabetic patients

[123]. Only 20% of patients undergoing amputation had ischemic gangrene (due to peripheral vascular disease) [124]. Due to cultural issues loss of a limb is considered worse than loss of a life in many African societies, indicating a complex problem [125].

Macrovascular complications

Macrovascular complications occur mostly in patients with T2D and are becoming more common, particularly in the urban setting with a Western lifestyle. In urban adults the prevalence of hypertension is 14-16% and obesity varies from 3-44% according to the level of urbanization [126]. Ischemic heart disease (IHD) includes angina, coronary artery disease and heart failure. It was until recently thought of as rare is SSA but studies have proven otherwise; IHD is present in 5-8% T2D African patients [114] and 4.8% of the patients had IHD present at diagnosis of diabetes [104]. Cardiomyopathy was reported in 50% of T2D patients [124]. Cerebrovascular disease in a Sudanese population was found in 5.5% of patients with IDDM [116]. Diabetes is present in more than one third of patients presenting with coronary events and close to 15% of people with stroke have diabetes [124].

7.2. PART 2B: Diabetes in Norway

7.2.1. Public health in Norway

Norway maintains a Scandinavian welfare model with universal health-care, subsidized higher education and a comprehensive social security system. The health care system is organized into first-line services, second line services and specialized referral hospitals. The general practitioner provides the first line service. In 2004, a new system was implemented where all citizens choose one doctor to be their contact person and each doctor has about 1000-2500 patients on his list. The general practitioner refers patients to specialist doctors in the second line service and a few is referred to the specialized hospitals. There are close to 80 second line hospitals in Norway and 26 of them have a pediatrics ward.

UUH is a second line hospital and the largest hospital in Oslo, the capital of Norway. All children with diabetes from the surrounding districts (Oslo, Asker and Bærum) travel to this hospital. The area has a total population of 700 000 people. UUH has the biggest department for diabetic children in Norway with close to 300 patients at follow-up every year.

7.2.2. The Norwegian Childhood Diabetes Registry

The Norwegian Childhood Diabetes Registry (NCDR) was established in 2006. NCDR includes data collected prospectively from 1989 and retrospectively from 1973-82. One of the aims is to standardize and optimize diabetes care throughout the country. Registration is voluntary and the children (or

parents, or both) have to give consent twice; once at diagnosis and once when the patients reach 18 years. Annually the NCDR publish a report, addressed mainly to the different hospital pediatric units responsible for the diagnostics and follow-up. The hospitals are marked with different codes that only the register and the hospital know. In this way hospitals can compare results (HbA1c values, epidemiology and insulin administration forms) with other hospitals. In 2009, the register included all 26 pediatric wards in Norway and included both time of diagnosis and follow-up data. 2314 patients (2299 T1D) participated in the annual control, which is estimated to be 92% attendance [25]. Almost all children with diabetes in Norway are registered in this registry and in 2009 only nine out of 361 newly diagnosed patients did not want to register [25].

Patient organization

The Norwegian Diabetes Association is a voluntary, independent patient organization for children and adults with diabetes and a member of IDF. It was founded in 1948 with the objective of serving people with diabetes and others that has an interest in the subject/disease. Today, the organization is located all across Norway with 150 offices and more than 40.000 registered members.

Diabetes Mellitus in Norway

Diabetes is a common disease in Norway, out of 4.9 million inhabitants, 375 000 [127] people have diabetes. The majority (93%, 350 000 people) have T2D, representing a fourfold increase over the last 50 years and it is believed that half of these have diabetes without knowing it. Estimated prevalence for T2D is 7% and 6 to 7000 people are being diagnosed with T2D every year; mainly people older than 40 years [127].

The rest (25 000 people) are diagnosed with T1D, giving a prevalence of 0.5%. T1D is often diagnosed during childhood and it is the second most common chronic disease (after asthma) in children in Norway; total number is 3300 children under 18 years [127]. Approximately 300 children in Norway younger than 15 years get diagnosed with T1D every year, which represent a doubled the last 30 years.

7.2.3. Epidemiology of diabetes at Ullevål University Hospital

In childhood, the distribution between T1D and T2D is quite different from the adult population. T1D accounts for 92% of diabetic children younger than 18 years, T2D 2.1% and MODY 6% (2009) [25]. Norway has one of the highest incidences of T1D in children and adolescents in the world with 36 per 100 000PYR (2009) [25]. The incidence has been increasing since the first registration by Westlund [128] who estimated the average incidence under the age of 20 years to be 9.8 per 100 000 PYR during the period from 1925-1954. Joner et al. [129] found an incidence of 22.4 per 100 000 PYR from 1989-1998.

In 2008, 27 newly diagnosed children with T1D in Norway were diagnosed at UUH. T1D was

diagnosed in all age groups with a peak between 13-16 years (figure 1) [25]. The incidence increased in 2009 with 48 patients being diagnosed with diabetes.

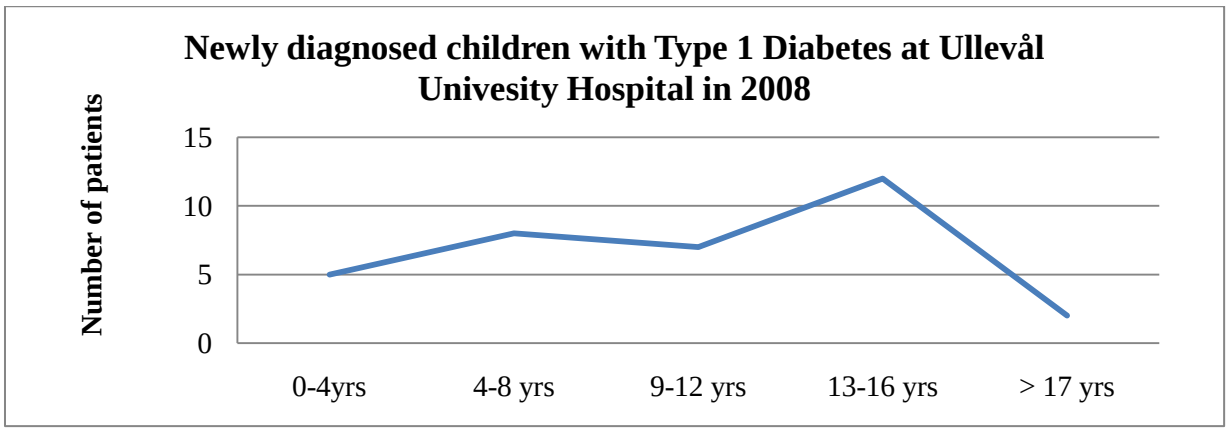

Figure 1: Age distribution among newly diagnosed children with Type 1 Diabetes at Ullevål University Hospital in 2008.

7.2.4. Treatment of Type 1 Diabetes at Ullevål University Hospital

All newly diagnosed children with T1D are admitted to hospital at diagnosis regardless of their condition. The average length of stay is eleven days. How long they are hospitalized is dependent on their socioeconomic status, how fast they learn how to deal with their diabetes and how comfortable they are with the administration procedures. The key point in Norwegian diabetes care is that the children with diabetes are the experts on their disease; the doctor is more an advisor. A multidisciplinary team is responsible for treatment and follow-up of children with T1D. In this team there is a doctor (paediatrician), a diabetes nurse (specialized education for 1.5years), a psychologist, a nutritionist and a social worker. The hospital has access to interpreters if the patients do not speak/understand Norwegian or English. If interpreters are involved, the duration of hospitalization is usually longer because of difficulties with communication.

The nurses are experienced with diabetes and they are specially trained to be able to educate. Most of the education at UUH is individual; group education at diabetes onset is difficult because relatively few get diagnosed at the same time. At the hospital, soon after diagnosis, the patient and the family is offered an appointment with a social worker and a psychologist. The social worker can help the family with the rights and different funding arrangements which they can claim.

Carbohydrate counting is used systematically. The children and family learn about nutrition and healthy food and the effect carbohydrates will have on the BG. The most important thing is that the children learn how to count carbohydrates in food and set insulin related to the amount of carbohydrates ingested. All children are recommended to eat healthily and to have a diet composed of many different kinds of nutrients, without strict restrictions on unhealthy food.

Type 1 Diabetes - Insulin therapy

At UUH 62% of the patients were on insulin pumps in 2009, compared to 52% nationwide [25]. All new onsets are offered to start with the pump at diagnosis and 98% of these patients start on a pump. The rest of the patients at UUH (38%) are on MDI therapy. The pen is the most common administration form (> 99%) with only a few patients using syringes. MDI is most often a combination of a long acting analog as Levemir or Lantus and a short acting analog, usually NovoRapid. Patients inject at least four injections daily. Nationwide, 65% use the pump in the youngest age group (younger than five years old) [25], with the lowest percentage (47.5%) in the oldest age group (15 years or older). In puberty the patients have increased need to not be different from peers, which can lead difficulties in measuring blood glucose and insulin injections. The insulin pump is especially important if the child is very young (less than six years old) because these children often need very little insulin, especially in the honeymoon-phase. It is easier to give diluted insulin through a pump.

Follow-up at Ullevål University Hospital

Follow-up is once every three months at the OPC and at this appointment the patients see a particular doctor each time, who is also the contact person. In between regular follow-ups, the diabetic nurses are available on the phone and many "everyday problems" are solved this way. At follow-up the doctor and the child discuss together with the parents, the challenges in the insulin/diabetes care. The patients are told to write down all BG measurements during the day. The doctor uses this as an instrument in changing the insulin dose and to give advice on how to obtain better glycemic control.

The parents are asked to participate in the treatment and the follow up of the child, at least until the child is 16-17 years old. The children attend their appointments without their parents more frequently when they get older (16-18 years old). The hospital wants to involve the parents even after the age of 16 years, so they are encouraged to attend the appointment with their child at least once a year. How much the parents participate and are involved, depend on how much responsibility the child takes and how much the parents want to be involved. The parents receive 14 days financial support for education and supervision in diabetes control at the time of diagnosis. During this period the parents can learn how diabetes works how to administrate insulin and learn and how to recognize symptoms of high and low blood sugar. Both parents are involved, to avoid one of them becoming "the expert".

Guidelines of childhood onset Type 1 Diabetes in Norway

National and UUH guidelines of childhood T1D are based on ISPAD's guidelines [1]. The treatment goal for HbA1c is less than 7.5% for children under 18years. In 2008, 17.3% of the patients reached their treatment goals.

7.2.5. Complications of Type 1 Diabetes in Norway

There is a screening program for autoimmune diseases and late complications. The screening for autoimmune diseases is performed annually for celiac disease and hypo- / hyperthyroidism. In 2009, nationwide, 98% of the patients were screened with a blood sample for celiac disease and 98% were screened for hypo-/hyperthyroidism with serum thyroid stimulating hormone (TSH) [25].

Late complications

Screening for late complications such as retinopathy, nephropathy and neuropathy is performed annually from: the age eleven years (in subjects diagnosed with diabetes for more than two years) or from age nine years (in subjects diagnosed with diabetes for more than five years).

Retinopathy

Retinopathy is tested by an ophthalmologist with fundal photography or ophthalmoscope. At UUH in 2009, 0.2% of the diabetic patients younger than 18 years had DR at follow-up in 2009. In a nationwide cohort of patients diagnoses with childhood diabetes from 1973-82 [66] DR was reported in 89.1% of T1D patients (mean diabetes duration of 24 years), of whom 31% had PDR. In T2D adult subjects 15 % had DR after mean diabetes duration of six years [130].

Nephropathy

Nephropathy screening involves a urine sample. At UUH in 2009, microalbuminuria (albumin/creatinine ratio > 2.5 mg or albumin excretion rate > 20µg/min) was found in11%, persistent microalbuminuria was found in 0.6% and proteinuria in 0.4% of the diabetic patients under 18years. After mean diabetes duration of 24 years, overt nephropathy was found in 7.8% of T1D patients diagnosed at 0-14 years in 1973-82. Persistent microalbuminuria was found in 14.9% of the subjects [131]. In this study 43% of the subjects with microalbuminuria were treated with angiotensin converting-enzyme inhibitors or angiotensin receptor II blockers, to avoid progression from microalbuminuria to overt nephropathy. Microalbuminuria is also associated with increased cardiovascular mortality and morbidity. After six years mean diabetes duration of adult T2D, 16 % developed DN [130].

7.2.6. Mortality of Type 1 Diabetes in Norway

Childhood T1D carries a fourfold increased mortality risk when compared with the background population in Norway [132]. Overall mortality rate was 2.2 per 1,000 PYR in subjects diagnosed with childhood diabetes [132]. Survival rate was 98.9% at ten years and 94.6% at 25 years [132]. The main cause of death in individuals older than 30 years of age was cardiovascular disease. The most common cause in young patients younger than 30 years was acute metabolic complications [132]. Violent deaths, suicide and intoxication were responsible for 29% of the total deaths.

7.2.7. Quality of life in children with diabetes in Norway

Patients with chronic diseases will be affected in their daily life. However, at UUH it is emphasized that the children are not diabetics; they are children with diabetes. Children with diabetes have to organize and structure their day differently than non-diabetic children. However, with good metabolic control, diabetes should have minimal affect on everyday life situations.

T1D can have severe consequences if insulin dosage is miscalculated and many parents risk becoming overprotective towards their children. Sometimes children with diabetes develop anxiety and avoidance of activities that they would have participated in if they did not have diabetes. To avoid situations like these, the patient receives assistance (information and education) in relation to school, hobbies and sports. Soon after diagnosis, the nurses offer to go out to schools and kindergartens and educate teachers/caretakers about diabetes. From the third grade the nurses go in the classes and teach the pupils about diabetes if a child in the class has this disease. The teachers learn about: diabetes in general, insulin and how this works and about hypoglycemia and what to do if this happens. They are also taught how to roughly count carbohydrates and how to find the right insulin bolus in relation to food, this way they can observe the children when he/she set their insulin and see if the insulin dose they are about to give seems reasonable. The teachers are allowed to give insulin if the child uses a pen or a pump. Most of the children in school are on pumps, the school nurse are very little involved in daily diabetes care Usually one school nurse works at four to five different schools and does not have the time to proper follow-up.

The parents are often involved in deciding daily insulin dosage; either they make a form with insulin boluses in relation to BG, or they are available on the phone as many children have cell phones and can call their parents before a meal to get help. The parents are responsible for teaching activity leaders/sport coaches, especially how to handle hypoglycemia (the hospital has special information brochures). If there is an interest the leaders/coaches/teachers can visit the hospital and get education from a diabetes nurse, or they can get some information about the disease over the phone.

The hospital arranges re-education for the patients. Once a year they have a group for girls about nine to ten years old and all children get re-educated at the age of twelve years. The aim for these meetings is that the patients can meet other people in the same situation and learn that they are not the only ones with diabetes. The parents also discuss problems and experiences around having a child with diabetes. In Norway, they are conducting research on the quality of life among children with diabetes. In 2009, a big study on the quality of life was initiated; this project will keep on going in 2010.

8. PART 3: Public health and diabetes in Rwanda – a partly personal observational study

8.1. Public health in Rwanda

The structure of the health care system in Rwanda is organized into 34 district hospitals and five reference hospitals; two university hospitals, one military hospital, one psychiatric hospital and a hospital whose mission is to provide specialized services not available in the other reference hospitals in order to limit the cost of evacuations outside the country [133]. Local health care centres provide first line service. They are run by nurses with a license to prescribe medication such as antibiotics, anti-malaria medication, antipyretics, anti-inflammatory, analgesics and proton pump inhibitors. The health care centres refer patients to the first line hospitals. Patients who cannot receive proper treatment here have to be referred to a second line hospital. Communicable diseases constitute 90% of chief complaints in health care facilities [133]

The share of the budget allocated to the health sector increased from 3.2% in 1996 to 12% in 2009 [133], which is still lower than the 15% target as other nearby countries with same level of economy achieve. However, 4/5 of the budget (58.6 billion RwF~7 billion EUR) is devoted to the offer of services and only less than one-fifth to administration. 75% of the doctors were in the city of Kigali, where approximately 15% to 20% of the entire population lives. 75% of the population lives within less than five kilometer from a health care facility.

WHO estimated that 30,000 people had diabetes in Rwanda in 2000 and predicted that by 2030 the prevalence would reach 77,000 people [134]. There has neither been established an official diabetes registry in Rwanda of childhood diabetes nor of diabetes in general. However, Association Rwandaise des Diabétiques is a Rwandan patient organization. One of their partners, Fraternité, publish free of charge leaflets providing basic information about diabetes to hospitals, dispensaries, and health care centres. Though tiny in comparison, such awareness-raising initiatives are effective in saving the lives.

Due to lack of data, this case study provides some facts about childhood diabetes care in Rwanda.

8.2. Case study

Data was collected retrospectively for all diabetic children diagnosed at or before the age of 15 years, who were admitted to the Department of Pediatrics at UTHB in Rwanda from October 2008 to October 2010. Patients older than 15 years were treated at the ward for internal medicine. Patients were referred from district hospitals in the Butare region or from community health centres via district hospitals. Diabetic children in Rwanda were routinely admitted to reference hospitals at the time of diagnosis for initiation of insulin therapy and stabilization of metabolic control. After discharge from

hospital, they were usually seen at the OPC once every month if their metabolic condition was stable and satisfactory. They are encouraged to seek medical help if they became sick due to diabetes or from other reasons.

Diagnosis of DM is based on elevated plasma glucose (p-glu > 200 mg/ml or >11,1mmol/l) combined with clinical manifestations of diabetes; polyuria, blurring of vision, polydipsia, weightloss, glucosuria and ketonuria. Ketoacidosis is diagnosed on clinical grounds in acutely ill patients with impaired consciousness, dehydration, acidotic breathing, hyperglycemia and glucose in the urine and on one occasion ketones in urine. Bicarbonate and pH is not measured. None of the patients died while being admitted to hospital. The BG is measured in g/dL from a venous blood sample, analyzed at the hospital laboratory, however, on rare occasions the nurses use a glucometer. The value in g/dl is divided with a factor 18.01 to get the value in mmol/L.

The patients with a persistently poor metabolic condition, other severe illnesses and those presenting with complications are re-admitted to hospital. The Department of Pediatrics keep careful register of all admitted patients including patient name, date of birth, date of admittance/discharge and diagnosis at discharge. Clinical records are stored in the archives and it is due to this method of registration only possible to retrieve those who had diabetes as diagnosis at discharge.

In the observational period at the ward for internal medicine, two patients with severe foot ulcers as a complication of T2D were admitted, both around 30 to 35years of age.

8.3. University Teaching Hospital of Butare

UTHB have 7060 inpatients per year and 30 915 outpatients per year (2010) (personal comm. hospital administration). The hospital has a ward for internal medicine, surgery, gynaecology and obstetrics and paediatrics. 1,8mill people live in the area of UTHB [135]. According to the National Commission of Poverty Reduction, the three provinces covered by UTHB are the poorest of the territory, though the general standard of Rwandan health care is poor, for example, there are only two dialysis machines (at UTHB and in Kigali) and only one CT scan in the country (Kigali). To get dialysis one has to write a personal letter to the president, who is the only one who can give permission. There was an electrocardiogram (ECG) machine at the hospital I worked in, though; during the observation period of seven weeks there was no ECG-paper.

Specialist training has been challenging since there are relatively few specialists in Rwanda. It is common that specialists from surrounding countries (or from European countries) come to Rwanda for a shorter or longer period of time to teach graduates.

The Paediatrics ward

The pediatrics ward has two rooms with 13 and 14 beds in each room, 27 beds in total. The ward is rarely overloaded. Three pediatric specialists, six post graduate doctors, two generalist doctors and

four internship doctors work at the ward. The interns have the main practical responsibility, but the senior doctor can give advice. Once a week all the doctors, interns, medical students and nurses do a ward round lead by one of the specialists, Professor Iraka. The interns rotated having the evening and night shifts together with one post graduate doctor. Five nurses worked at daytime, two during the evening/night shift. The nurses speak mainly French, the doctors speak mainly English and the patients speak mainly Kinyarwanda (local language). The majority of nurses and doctors speak Kinyarwanda, except a few foreign doctors. This language conflict is a result of the shift from French to English as official language in 2007. Nurses educated before 2007 have, therefore poor, knowledge of English. Professor Iraka is one of three specialists at the Pediatric ward at UTHB. He is a dedicated professor and highly acknowledged by colleagues and medical students. He is originally from Uganda, where he took his medical degree but has been working for the past three years in Rwanda at UTHB.

8.4. Guidelines diabetes care at the University Teaching Hospital of Butare

There is no specific protocol for diabetes care at UTHB (personal communication professor Iraka). The doctor is in charge of everything concerning the treatment; fluids, electrolytes and insulin, both in the acute phase and during follow up. The nurses inject the insulin and draw blood for testing. The nurses do not make adjustments. Relatively few day to day symptoms are noted in the patient records. For acute management of *DKA*, the guidelines used at UTHB are described in the book "Pediatric Emergencies", by Francois DeVilliers (personal communication professor Iraka).

8.5. Results

Epidemiology

The hospital records of eight children (eight records) with T1D were found out of eleven registered patients. Total number of registered files was 15 due to several re-hospitalizations. All patients fulfilled ISPAD and WHO criteria for diagnosis of T1D in children [1,35]. In the observation period from November 2008 to October 2010, four new onset T1D cases were registered (table 3). All four patients were diagnosed in 2010, none in 2009. The other four were due to re-hospitalization (diagnosed T1D 3-5 years earlier). All patients were prone to ketoacidosis and required insulin for survival. In this group, there were four girls and four boys giving a male: female ratio of 1:1. The mean age at diagnosis was 10.2 years; 10.9 years for female, and 9.5 years for male. A history of known T1D in a close relative (the mother) was reported by one (12.5%) patients. Local standards on growth and pubertal development are unknown but many of the children (both new onset and re-hospitalisation) were reported to be under the third percentile.

Table 3: Comparison between epidemiology in childhood diabetes care in Rwanda, represented by University Teaching Hospital of Butare (UTHB) and Norway, represented by Ullevål University Hospital (UUH) in 2009. UTHB classify children under 15years, while UUH classify children under 18 years. T1D=Type 1 Diabetes. T2D=Type 2 Diabetes

	University Teaching Hospital of Butare (2009)	Ullevål University Hospital (2009)
Total diabetic patients hospitalized	3	-
New onset diabetes patients	0 (4 in 2010)	48
Newly diagnosed T1D patients	0 (4 in 2010)	44
Newly diagnosed T2D patients	0	1
Newly diagnosed MODY patients	0	3
Age at onset (years)	10.2 (3.5-14)	8.1 (0.4-14.9)
Duration of first time hospitalization (days)	33	11

One patient became diabetic at 3.5 years and the oldest at the age of 14 years. Three patients were diagnosed between ages 4-11.5 years (pre-puberty) and four patients between 11.5-15 years (puberty). Duration of symptoms before diagnosis ranged from four days to two months with a median of 20 days. Mean BG at hospitalization was 21,7mmol/L. Mean BG at discharge was 12,0mmol/L. The highest measured BG for all patients was 35.5mmol/L and the lowest was 0.6mmol/L. All patients had huge swinging values from day to day, but also during the day. Mean duration of hospitalization for first time hospitalizations was 33 days, the shortest was 25 days and the longest stay was 37days. The mean duration of re-hospitalization was 19 days.

Table 4: Diabetic ketoacidosis in children with Type 1 Diabetes in Rwanda represented by University Teaching Hospital of Butare and in Norway, represented by the Norwegian Childhood Diabetes Registry in 2009 compared to ISPAD Guidelines. Rwanda classify children under 15years, while Norway classify children under 18 years.

	University Teaching Hospital of Butare	Norwegian Childhood Diabetes Registry	ISPAD Practical Guidelines 2010
DKA diagnostic criteria	Clinical symptoms	Clinical symptoms and biochemical criteria	Clinical symptoms and biochemical criteria: Hyperglycemia (BG >11 mmol/L [≈200 mg/dL]), venous pH <7.3 or bicarbonate <15 mmol/L, ketonemia and ketonuria.
DKA at onset (%)	100	25	As few as possible
Patients re-hospitalized with DKA (%)	Unknown	5	As few as possible

All first time hospitalized children (100 %) and two (50%) of the re-hospitalized patients presented with DKA (table 4). Symptoms and clinical findings for the re-hospitalized patients varied greatly from lung crepitations, failure to thrive, hepatomegaly, jaundice, dark urine, edema, caugh, systolic murmur, gallop rhythm, raised jugular vein pressure (JVP), acites, subcostal retractions, and epileptic seizure. First time hospitalized patients showed little signs of other organic or chronic disease (fig. 2).

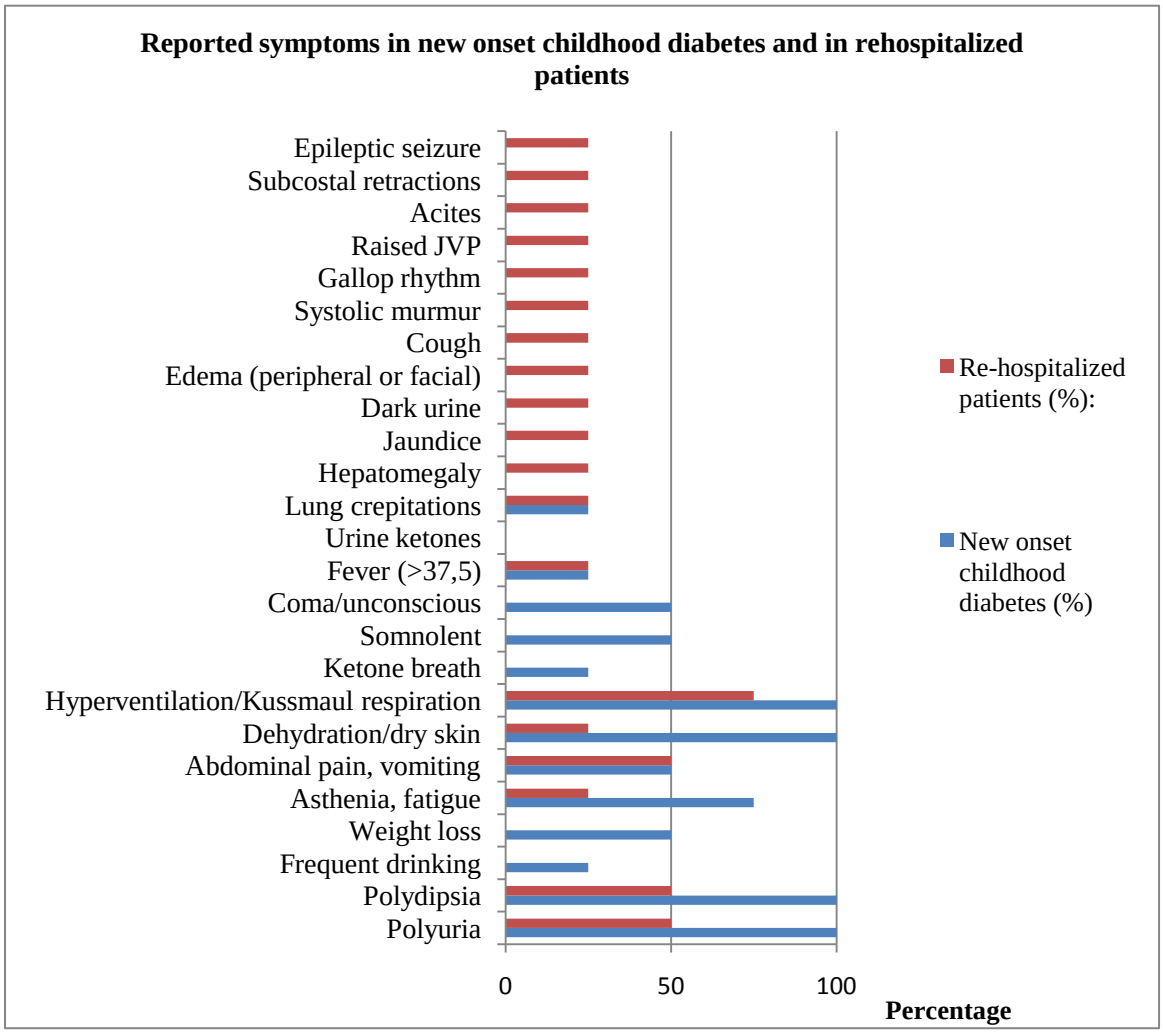

Figure 2: Reported symptoms at admission to hospital in the eight case reports. One patient can have many symptoms.JVP= jugular vein pressure.

Mortality

The following section is based on personal communication professor Iraka. Surveys on mortality rate due to diabetes have not been performed in Rwanda. From experience, life expectancy for people with diabetes is 30 to 35 years old, many of them die as teenagers as well. It is difficult to say how many children die from DKA at home and how many children die from DKA at the hospital; in general it is reasonable to assume that most kids die from DKA at the district/university hospital, not at home. This makes it difficult to estimate mortality rate. If the parents recognize it as DKA or an acute illness that needs hospitalization, not many patients die before reaching the hospital.

Incidence

According to experience there has been an increasing rate of DM over the last three years at UTHB. UTHB drain 1.8 mill people, half of these (770 000) are younger than 15 years. Diabetes is still an unknown disease, but in general people are getting better to seek professional medical care and there is greater awareness on health (personal communication professor Iraka). Based on four cases of new onset T1D in 2008-10, estimated mean annual incidence would be 0.3 per 100 000 PYR (table 5), which is among the lowest incidences in the world.

Table 5: Incidence rate in childhood diabetes in Rwanda (estimate based on this study, mean annual incidence 2008-10) and in Norway [25] in 2009.

	Rwanda (2008-10)	Norway (2009)
Incidence rate (per 100 000 patient-years)	0.3	36

Treatment

All of the patients were treated with regular insulin and the most common regime was the combination of Actarapid (rapid acting regular insulin) and Ultratard (long acting regular insulin) (87.5%) (table 6). One patient (12.5%) was treated with intermediate acting insulin combined with rapid acting. All patients (100%) were given two injections per day (figure 3); 2/3 of total dose was given before breakfast (2/3 long acting, 1/3 rapid) and 1/3 of total dose before dinner (2/3 long acting, 1/3 rapid). Intermediate acting insulin was preferred over long acting but seldom available at the pharmacy. The ideal regime consisted of three injections per day but it was observed poorer compliance and outcome and thus, injections twice daily was re-established (personal communication JWO Iraka). All patients used syringes to inject insulin.

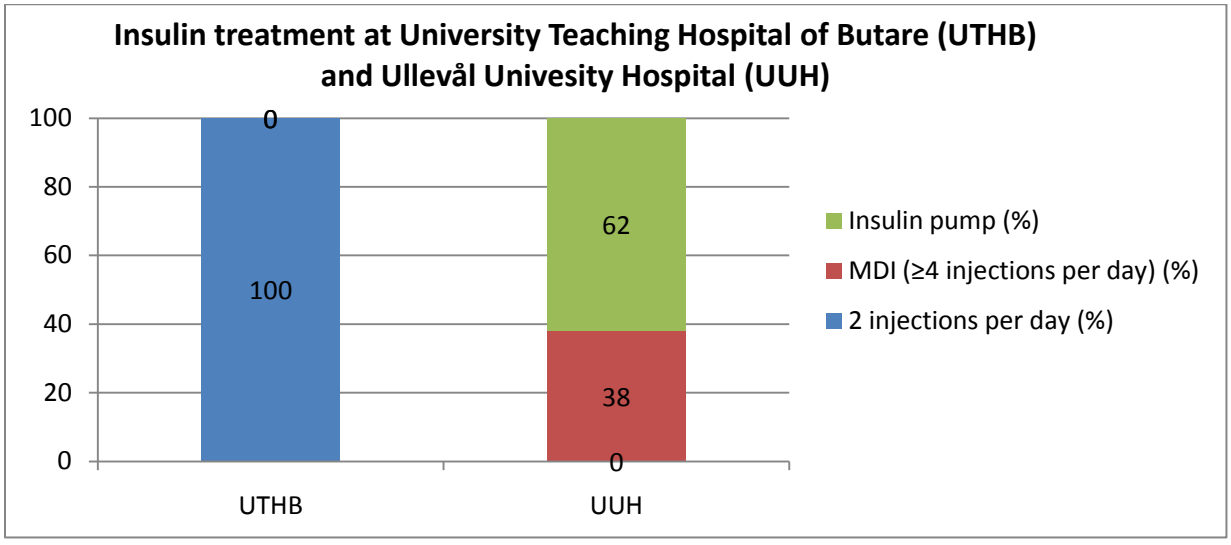

Figure 3: Insulin treatment regime in Rwanda University Teaching Hospital of Butare and in Norway at Ullevål University Hospital in 2009.

Table 6: Insulin treatment in children with Type 1 Diabetes at University Teaching Hospital of Butare (Rwanda) at Ullevål University Hospital (Norway) in 2009 compared to ISPAD Guidelines. ISPAD=International Society for Pediatric and Adolescent Diabetes.

	University Teaching Hospital of Butare	**Ullevål University Hospital**	**ISPAD Practical Guidelines 2010**
Ultralente (long-acting) + ActaRapid (regular soluble) (%)	87.5	0	Intermediate acting insulin should be available to all patients. Analogs are preferred over regular and traditional insulin.
Monotard (intermediate acting) + ActaRapid (regular/soluble) (%)	12.5	0	
Levemir/Lantus + NovoRapid (analogs) (%)	0	100	
Self adjusting the dose (%)	0	100	Recommended

The mean number of measured BG value (in hospital) was 1.4 times per day. It is difficult to avoid swinging values with only one or two BG measurements a day, especially in a new environment (hospital) where other factors could influence BG such as abnormal food intake, low level of physical activity and concurrent infections. Home blood glucose monitoring was not used and simple urine glucose testing was not performed regularly. The price for a glucometer was 5000RwF (6 EUR) (including one month supply of strips), equal to 5-6 days of work. Even with the means to buy a glucometer it was experienced difficult to educate patients to be qualified to make dose adjustments. Thus, dose adjustments were rarely performed by the patients according to daily activities or other illnesses. In the first weeks after diagnosis, the average daily dose of insulin required to achieve reasonable metabolic control was 0.6-1,3IU/kg/d. At discharge the insulin dose varied little, from 0.9 IU/kg/d to 1.1 IU/kg/d. During hospitalization, it was many times reported that insulin was not given. Sometimes it was reported that insulin was not given because it was not available but most of the times the reason was not recorded. It was not possible to measure HbA1c at UTHB. In 2005, none of the medical centres in Rwanda were able to monitor HbA1c [51].

Acute treatment of ketoacidosis

Fluid replacement was given first; 500ml first hour, then at a slower rate. Insulin used for intravenous administration and sliding scale was rapid acting regular insulin. All patients started on hourly insulin infusions, switched to sliding scale and then to s.c injections. The mean time until introducing s.c injections was 3.6 days (range 1-8 days). First time hospitalized patients spent twice as many days before getting on s.c insulin as the re-hospitalized patients; 4.8 days (2-8) compared to two days (1-4).

Potassium was measured in three out of four (75%) of first time hospitalized patients and ordered in one patient (no records of it being measured). Hypokalemia was reported in two of the patients (2.1mmol/l, 2.3mmol/l, reference value: 3.5-5.1mmol/L). Potassium replacement (KCl) was given to one of these patients, not available to give to the other. This patient received KCl 20mmol/l/2h at the second day and 20mmol/l/12hour at the third day. The fourth day the patient had an episode of hypotension with cold extremities. There was not performed a control potassium after receiving the fist bag of KCl. Potassium was neither measured in the re-hospitalized patients.

Table 7: Diagnostic criteria for diabetes, treatment goals and follow-up at University Teaching Hospital of Butare (Rwanda) and at Ullevål University Hospital (Norway) in 2009, compared to ISPAD Guidelines. Rwanda classify children under 15years, while Norway classify children under 18 years. ISPAD=International Society for Pediatric and Adolescent Diabetes. HbA1c= Hemoglobin A 1 c. DKA=Diabetic ketoacidosis.

	University Teaching Hospital of Butare	**Ullevål University Hospital**	**ISPAD Practical Guidelines 2010**
Diagnostic criteria	Casual plasma glucose >11.1 mmol/l and symptoms	ISPAD Guidelines	One criteria out of three: 1. Fasting plasma glucose ≥7.0 and symptoms 2. Plasma glucose 2h after oral glucose tolerance test >11.1mmol/l 3. Casual plasma glucose >11.1mmol/l
Multidisciplinary team	Doctor	ISPAD Guidelines	Doctor, diabetic nurse, nutritionist, social worker, psychologist.
HbA1c	Not performed	Every 3. Months	Every 3. Months
Treatment goal	Not classified	HbA1c < 7.5%	HbA1c < 7.5 for children up to 18 years.
Follow-up frequency	Every month	Every 3.Months	Every 3. Months
Children at follow-up	Unknown	270	
Follow-up attendance (%)	Unknown	98	100

Follow-up and complications

The nurses taught the children how to do the poking. The patients went home with a follow-up every month at the OPC to get a new insulin prescription and they got insulin from the hospital pharmacy. This was a way of guaranteeing that the patients came back for follow-up. Most of them came back every month. In this region it is rare to have a refrigerator at home, thus, the usual way to store insulin is to bury it in the soil. Waiting time for an OPC consultation was often more than six hours and the

travel could take up to five hours each way (often by foot). One parent usually followed the child. It was uncertain how many patients who were lost to follow-up (personal communication JWO Iraka).

No information given to the families about the effect of the disease or quality of life could be detected from the records. One patient (12.5 %) was reported to have had discontinued his schooling because of the disease. There were no endocrinologists, specialized diabetic nurses, psychologists, nutritionists or social worker at the hospital (table 7).

Table 8: Complication screening at University Teaching Hospital of Butare (Rwanda) and at Ullevål University Hospital (Norway) in 2009, compared to ISPAD Guidelines. Rwanda classify children under 15 years, while Norway classify children under 18 years. ISPAD=International Society for Pediatric and Adolescent Diabetes. TSH=Thyroid stimulating hormone.

	University Teaching Hospital of Butare	**Ullevål University Hospital**	**ISPAD Practical Guidelines 2009**
Complication screening	Not performed	98% of patients screened annually for retinopathy and nephropathy	*Retinopathy:* fundal photography or mydriatic ophthalmoscopy. *Nephropathy*: urinary albumin/creatinine ratio or first morning albumin concentration. Annually screening, commence 2 years after onset for pubertal-onset T1D and after 5 years or age 11, whichever is earlier for pre-pubertal onset. *Neuropathy*: history and phys. examination. Unclear when to commence. *Macrovascular disease*: lipid profile every 5 years, blood pressure annually. After age 12 years.
Co-morbidity screening	Not performed	Screened TSH. 98% of patients was screened for celiac and hypo- / hyperthyroidism	Annually for autoimmune diseases; Celiac disease (blood test), hypo- / hyperthyroidism (TSH). Every third year screening for Addison's disease.

During hospitalization symptoms of severe hypoglycemia were reported twice but not classified as hypoglycemia in the files (measured BG 0.6 and 1.9mmol/L); decreased consciousness, no speech, and agitation. Hypoglycemia occurred usually as a result of low food intake (due to not having food or not wanting to eat) and after a too high dose of insulin. Hypoglycemia was reported once after a patient developed a fever. Long-term complications were not screened for or recorded (table 8 and 9).

Table 9: Figures on prevalence of diabetic complications in children with Type 1 Diabetes in Rwanda and in Norway in 2009. In Rwanda children are under 15 years, in Norway children are under 18 years). The Norwegian Childhood Diabetes Registry provides data for Norway and UTHB provides data for Rwanda. UTHB= University Teaching Hospital of Butare.

	Rwanda (UTHB)	Norway (Norwegian Childhood Diabetes Registry)
Retinopathy <18years	Unknown	0.2%
Persistent microalbuminuria <18years	Unknown	0.6%
Albumin/creatinine ratio > 2,5mg or albumin excretion rate >20µg/min <18years	Unknown	11%
Proteinuria <18years	Unknown	0.4%

Comparison of diabetic complications in Sub-Saharan Africa and Norway

Prevalence of DR is increasing along with longer duration of diabetes. Few longitudinal studies were performed. South Africa [89] reports significantly lower prevalence (59 %) of DR in T1D subjects compared to Norway (89.1%) [66] , mean duration respectively 24 and 23 years. In the South African study close to 50 % of the subjects were lost to follow-up and only 17 of the originally 88 survived to participate in the 20 year follow-up. Almost all original subjects in the Norwegian study participated in the follow-up. It is reasonable that many of the lost subjects had DR and true prevalence is probably higher. Among Tanzanian schoolchildren DR was higher in the pre-pubertal (4-11.5years) and post-pubertal (15.5-18years) group than the puberty age group (11.5-15.5years), indicating that some of the children died before puberty or were lost to follow-up for other reasons [109].

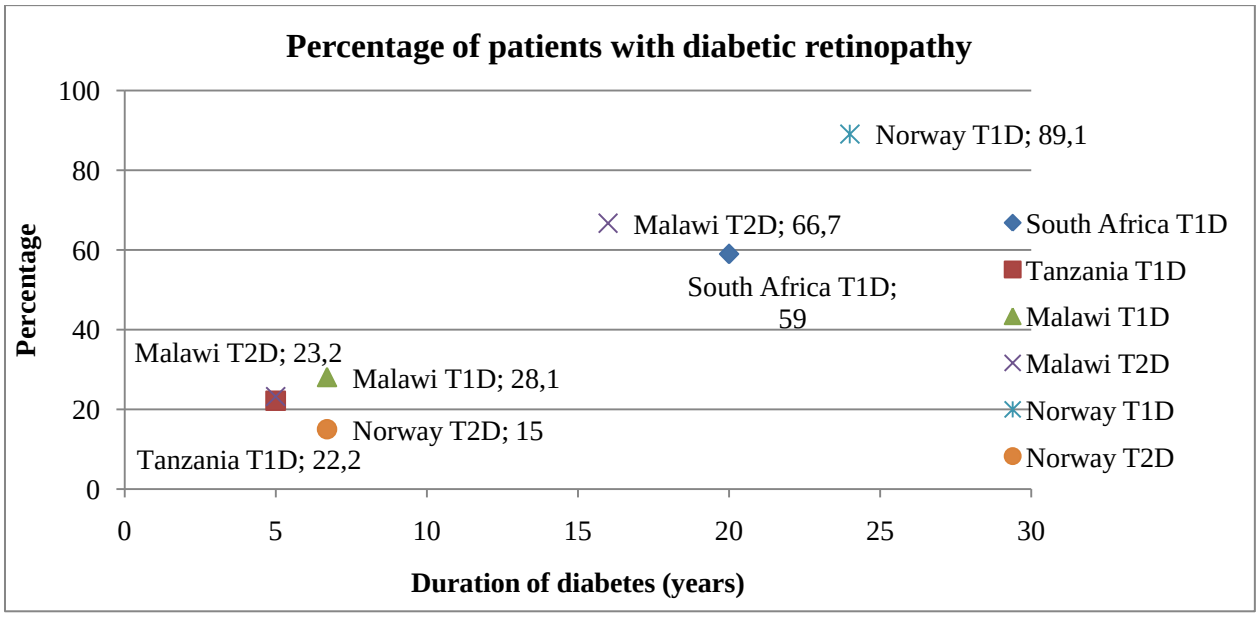

Figure 4: Comparison between Sub-Saharan countries and Norway and the development of diabetic retinopathy after a given duration of diabetes mellitus. T1D= Type 1 diabetes. T2D= Type 2 diabetes.

South Africa reports a lower rate of DN compared to surrounding countries (same confounder as mentioned above). Complication rate increases with longer duration. As the complication rate in SSA countries is higher at an earlier point than Norwegian subjects, it is evident that this difference will increase with longer duration. Microalbuminuria was found in twice as many Tanzanian and Ethiopian T1D subjects after five years as after 24 years duration of T1D in Norway. The rate reported from Ethiopia after ten years duration of IDDM is significant higher compared to the other countries.

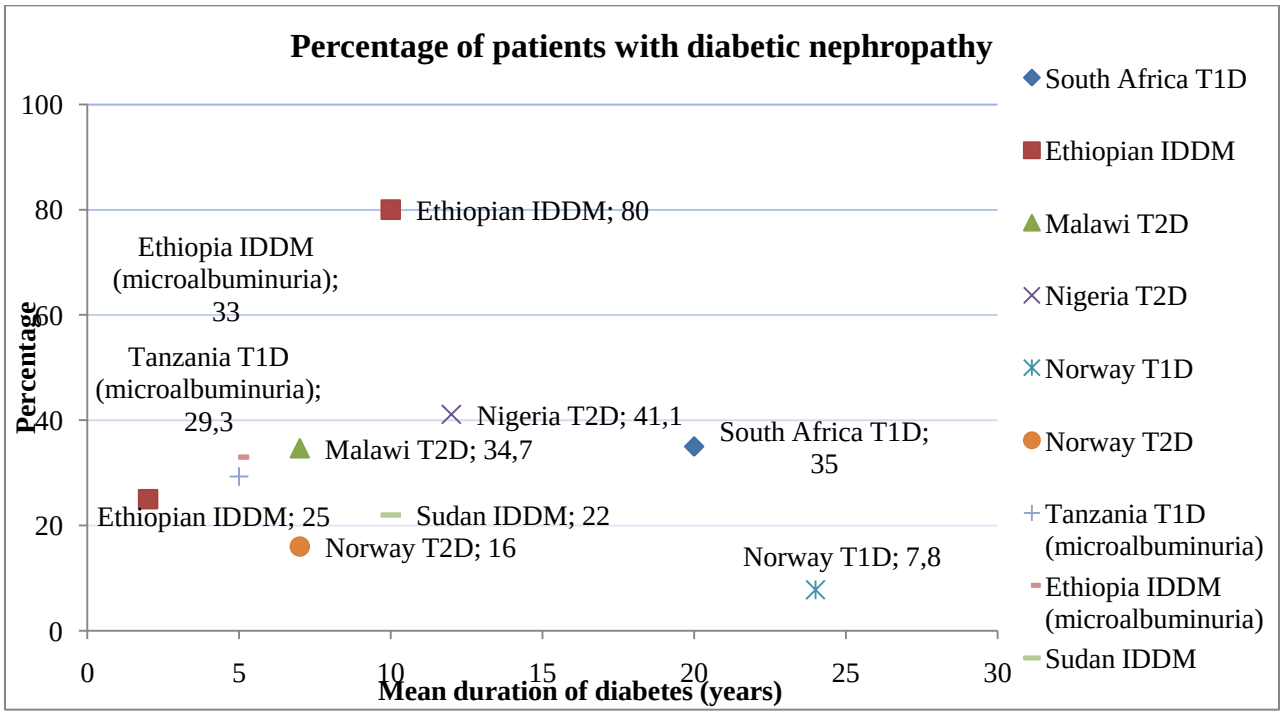

Figure 5: Comparison between Sub-Saharan countries and Norway and the development of diabetic nephropathy after a given duration of diabetes mellitus. Nephropathy is defined as having persistent proteinuria or albuminuria. Microalbuminuria is plotted for Tanzania and Ethiopia. IDDM= insulin-dependent diabetes mellitus. T1D= Type 1 diabetes. T2D= Type 2 diabetes.

9. PART 4: Comparison between Rwanda and Norway

Rwanda and Norway are two very different countries in different parts of the world. Rwanda is a small Sub-Saharan African mountain country with one of the highest population density in Africa. In comparison, Norway is 15 times bigger in size and has only 4.9 million inhabitants [136]. Table 10 list a few differences between Rwanda and Norway. Despite great economic growth and relatively stable political conditions in Rwanda since the Genocide in 1994, it is still considered a developing country. Life expectancy in Rwanda is 58 years (increasing rapidly from 39.9 years in 2003) [137] compared to 80.2years in Norway [137]. Norway is a democratic, constitutional monarchy located in the north of Europe as a part of the Scandinavian countries (Norway, Sweden and Denmark).

Norway is divided into 19 regional units and into 435 local municipalities. In the 1970s the discovery of the oil on Norwegian continental shelf transformed the country from a below median wealthy

country in Western standard to one of the richest countries in the world. Along with economic growth the standards of living became better and public health improved.

Table 10: Differences between Rwanda and Norway.

	Rwanda	**Norway**
Population (mill.) [136]	10.7	4.9
Population density (inhabitants per k m^2) [136]	420	16
Rural population [136]	80 %	25 %
Inhabitants per doctor	33 000 [133]	229 [138]
GDP ($ per capita) [136]	88.6 mill	535
Life expectancy [137]	58	80.2

9.1. The Rwandan Genocide

In the months of the Genocide in 1994 Rwanda received great international publicity. Genocide affected the entire population, and marked the Rwandan people for a long time after. Within three months in 1994 over one million Rwandan people got killed; the majority was brutally murdered with machetes. The background for the genocide was the longstanding conflict between the two main tribes in Rwanda; the Hutus (85% of the population) and the Tutsis (12%). A lot was blamed on colonialism, especially the Belgians, who initially introduced so-called racial cards in the 1920s. The racial cards caused the development of an unfair political and educational favouritism of the Tutsis at first and later (in the 80-90s) the Hutus. In 1994, the conflict culminated with a Hutu president being killed. The Hutus blamed the Tutsis and the killing started. What made this genocide even more special was that this happened in a society were Hutus and Tutsis traditionally lived peacefully side by side and suddenly neighbours murdered neighbours and husbands murdered their wives. During the genocide many women got raped by HIV positive men with the result of many HIV positive children.

The HIV/AIDS rate is currently declining due to successful anti HIV/AIDS campaigns but still the prevalence is around 3% [133]. Another challenge is that more than 600 000 children are orphans [133]. Many of them live together with other relatives, but for some all relatives died during Genocide, from HIV/AIDS or from other diseases. In 2009, there were 7 000 street kids in Rwanda. There are various reasons that a child becomes a street kid; some seek a better life in the bigger cities, some have lost their parents, others can't afford to go to school and end up on the street instead. These children are often rejected from their families, neglected by society, very few go to school and the crime rate is high. If diabetes was added to this picture, the expected outcome is poor.

9.2. Child mortality rate

Child mortality rate (CMR) is an indicator of the quality of general health and health care system in a country. Developing countries have in general a higher CMR than developed countries. In SSA one in eight children (12%) die before their fifth birthday. The United Children's Fund (UNICEF) estimated that CMR in children younger than five years in Rwanda was 200/1000 (20%) of live births in 2009. However, there were huge disparities between rich and poor households in developing countries. The high CMR in Rwanda stands in great contrast to the low CMR in Norway at 4/1000 (0.4%).

9.3. Discussion

Diabetes care in Norway and in Rwanda differs greatly and it is not possible to oversee the enormous difference in economic means. With this said, physicians and nurses in Rwanda deserves credibility for the effort and work despite lack of technological equipment, which reminds us about the importance of the good clinician. It is worth noticing that the total number of diabetic children seen by a Norwegian doctor is much higher (48 newly diagnosed each year at UUH compared to four patients the past two years at UTHB). Naturally, a physician that treats a large quantity of diabetic children will improve his clinical experience and obtain a better outcome for the patients. The DERI study confirmed this statement comparing clinics in Europe [26].

Epidemiology

The clinical presentation of childhood diabetes observed in this study of eight case reports from Rwanda is in accordance with classical symptoms of T1D [1]. None of the patients were obese and none of them showed any of the known features of T2D or atypical ketosis-prone diabetes. An interesting finding was that all newly diagnosed children received relatively high doses of insulin (0.9-1.1IU/kg/day). Insulin requirements are known to be less than 0.5IU in the remission phase and 0.7-1.0IU/kg/day outside partial remission phase and even up to 2IU/kg/day in puberty. No such distinction was found here but the doses are fairly equal to ISPAD recommendations. The high dose of insulin required at diagnosis combined with growth under the third percentile for some of them could indicate that these children had a different subtype of diabetes such as MRDM. As all children were prone to ketosis and DKA and otherwise presented a classical picture of T1D, it is unlikely these children had MRDM, though this need to be further investigated.

It is likely that there is an underestimation of diabetes in Rwanda, partly due to misdiagnosis (children presenting with diabetic coma are likely to be diagnosed with cerebral malaria or meningitis) [139] and partly because of the high CMR. A natural consequence of high CMR is that it becomes fairly common to lose a child in Rwanda; this is considered rare in Norway.

The age distribution of the patients demonstrated a peak around puberty (12-14 years), similar to findings in the DIAMOND study [14] and at UUH in Norway (peak between 13-16 years). Several

countries [18-20] reported that diabetes was frequently diagnosed in the younger age groups and South Africa, Tanzania and Ethiopia [92-94] reported a peak around 20 years. In this study the peak age of diagnosis in Rwandan children was 10.2 years, compared to 8.1 at UUH in Norway. No conclusions to support or disprove these trends can be made because: the material is limited, CMR is high (underestimation in the youngest age group) and because this study does not involve children older than 14 years.

T2D was observed among older patients and it is reasonable to believe that a distinction between T1D and T2D was done. This study involved very few individuals, therefore, any estimation of prevalence or incidence would be unreliable. Nevertheless, if estimated incidence is 0.3 per 100 000 PYR, this is very low. Adding the additional 70 to 85% which account for undiagnosed diabetes in many African countries [9], the numbers are still small. All new onset subjects in this study were diagnosed within the last eight months of the 24 months observational period, indicating a rising incidence. Local doctors supported this observation. Norway resides on the other end of the scale (36 per 100 000). The explanation for this unequal distribution remains unknown.

Treatment

At UUH, most children with T1D use insulin pump therapy, and the rest use MDI most commonly with a pen as administration form. In contrast, all children at UTHB use two injections per day and all of them use syringes. ISPAD recommends MDI or insulin pump therapy as the best options (equal regarding outcome and late complications) [47]. Two injections a day is acknowledged by ISPAD as a common insulin therapy regime in many parts of the world [47], though more frequently associated with poorer metabolic control and increased rate of complications [47]. ISPAD [47] and UTHB preferred intermediate insulin over long-acting insulin (in combination with rapid acting insulin) but due to not having intermediate insulin at the pharmacy, it is not used in the majority of the UTHB patients.

Complications and mortality

All patients (100%) had DKA at the time of diagnosis, compared to 25 % in Norway. Multiple reasons can explain this; people seek medical care later in the process, diagnostic misinterpretation and medical delay at health care centres/district hospitals. Poor prognosis of diabetes in Rwanda is reflected in the lower life expectancy: 35 years compared to 58 years in the background population [137]. Despite lack of reliable data, it is reasonable to assume that the life expectancy in Rwanda is shortened by more than 20 years due to diabetic complications. This is similar to life expectancy for a person with diabetes a few years after the introduction of insulin [8]. For a patient with T1D in Norway, survival rate in Norway was 98.9 % at ten years and 94.6% at 25 years [132]. In South Africa 20 years mortality rate was 43% (57% survival rate) [89]. These figures may highlight the inadequate facilities available for care of children with T1D in developing compared to developed countries.

Chronic hyperglycemia increase the risk of complications

Acute and probably also chronic complications of diabetes appear in Rwandan children, though complication rate is not registered. Short-term metabolic control is poor as shown by frequent hyperglycaemic episodes combined with great day to day BG variation. This finding is not surprising because the children do not always have insulin available and they do not self adjust the dose according to daily activities and food intake. Even when insulin is available, most of the patients lack the knowledge and means to administrate it correctly. In lack of means they take fewer doses of insulin to make it last longer.

There was a high rate of pathological clinical manifestations in the re-hospitalized group, even though the duration of diabetes only was three to five years. Direct diabetes related complications were not acknowledged in the records, but multiple organ pathologies may indicate both direct and indirect complications of diabetes (figure 2). Chronic elevated blood sugar increases vulnerability to infectious diseases [140] and represents co morbidity. Reported symptoms are likely to be consistent with different pathologies as hepatitis (hepatomegaly, jaundice, dark urine, edema, acites, raised JVP) and pneumonia (lung crepitations, caugh) in several of these patients. Arrhythmia could be related to rheumatic heart disease (systolic murmur, gallop rhythm) which is relatively common in Rwanda or autonomic neuropathy. Some symptoms could also be related to kidney failure and the hepatorenal syndrome (kidney failure as a result of liver failure; edema, raised JVP).

Insulin dose was adjusted during hospitalization where patients were relatively inactive and stayed in bed most of the day. Insulin requirements are known to be less during physical activity [141]. The daily routine for a Rwandan child, especially in the rural areas, includes long walks to school and heavy physical work on the fields. If the level of physical activity is higher at home this increases the risk of hypoglycaemic episodes. The patients are in general discharged with a higher BG than the recommended HbA1c under 7.5% would reflect (mean BG at discharge 12.0mmol/l equal to HbA1c at 9%). This could be a "calculated too high BG" due to the natural decrease in BG with increased level of activity at home or because a chronically too high BG was considered better than having many hypoglycaemic episodes.

Insulin is not always available in Rwanda

ISPAD recommends that all children with diabetes should at least have access to intermediate insulin combined with rapid acting/regular insulin; due to lack of availability, this is not possible in Rwanda. Insulin treatment is mainly based on long-acting insulin in combination with rapid acting regular insulin. Analogs have shown to reduce hypoglycaemic episodes and are considered better, but as they are 50-100% more expensive, it is understandable that implementation is not possible in Rwanda.

In 2005, the president of the Association Rwandaise des Diabétiques, F. Gishoma, published an article [51] to highlight the main problems in diabetes care in Rwanda. He emphasized the importance of

availability of insulin and the need for international co-operation in making insulin available for developing countries that are not able to compete with international pricing. The average daily income of most Rwandan people is less than 1.0 EUR, a visit to the family doctor costs around 4.0-5.0 EUR and a visit to a specialist 8.0-10.0 EUR [51], equal of the average person's income for one week. These estimates are not unreasonable in 2011. A stay at the hospital causes a great financial burden upon a family. The cost for having a child in hospital is double; both the direct cost of 3000-4000RwF (4-5 EUR) (with health insurance) and the additional loss of income because one of the parents have to stay at the hospital together with the child. The hospital is in most cases far from the patient's home, making a combination impossible. UNICEF reported that 88 % of women in Rwanda have to walk for more than one hour to reach any kind of health care facility. Diabetes care was only offered at the university hospital which meant up to six hours travel (often by foot) to get there, each way. It is necessary with good health to walk for several hours to get to the OPC, thus, a selection has already been made.

Gishoma [51] states that the excessive cost of insulin and diabetes supplies remains a major threat to the health of most people with diabetes. The withdrawal of animal insulin and the introduction of more expensive human insulins exacerbated the threat even further: a vial of human insulin 100 U/ml (~three months supply) costs around 15.0 EUR. He suggests that as a result, many people who should be taking carefully managed doses of insulin are forced to use inappropriate medication or seek care from traditional healers. In 2005, Australian "Insulin for Life" and IDF Child Sponsorship Program offered their partnership to Rwanda. If these organizations still provide insulin today is not certain, but NovoNordisk project (Denmark) was established recently to provide free insulin supply. However, the patients still have to pay the OPC registration fee of 700RwF (~1EUR) once a month to get the insulin prescription.

Closer cooperation between doctors and nurses can improve diabetes care

Health systems in sub-Saharan Africa are currently organized for the treatment of acute rather than chronic conditions [142]. It is true that Rwanda needs more doctors instantly and that lack of means makes it difficult to prioritize expensive treatment for chronic diseases in a picture dominated by acute infectious diseases. There could be more efficient ways to tackle the escalating double burden of diseases in the future. In traditional diabetes care the doctor has all the responsibility and the nurses assist. This has been and still is the situation in some Norwegian hospitals today as well as in Rwanda. At UUH and several other hospitals, there has, however, been a shift towards making the nurses more independent in both teaching and follow-up of the diabetic children. In countries where there are few doctors per inhabitant, special trained diabetic nurses could lighten the burden on the doctor.

Quality of life

Many children and adolescents find it difficult to cope emotionally with their condition. Diabetes causes them embarrassment, results in discrimination and limits social relationships. It is alarming that one of the diabetic children in Rwanda quit school because of diabetes. When a child gets a chronic disease such as diabetes, it affects not only the child itself, but the whole family in multiple ways; financially, socially and quality of life. Families with more than ten children are fairly common in Rwanda. If a huge part of the family's budget has to be spent on expensive diabetes treatment for one of the children, it is likely to believe that this could mean less food, less clothes and/or discontinued schooling for the siblings as well. In Norway, the major single cause of death in T1D subjects was due to violent deaths, including accidents, suicide and intoxication, indicating the psychological vulnerability and excessive burden it is to have diabetes.

9.4. Conclusion

Diabetes is still a neglected disease in Rwanda, though, greater awareness and knowledge is rising. As the situation is today, optimal diabetes care in depends on international funding of insulin and governmental action to put chronic diseases on the agenda. Construction of specialized diabetes clinics and trained health care personnel are needed as well as an official diabetes registry. Even though Norway has a solid skeleton of diabetes care, we still face many challenges and there is need for further improvement in glucose control and decreased complication rate. Other aspects of having diabetes need to be more thoroughly explored in the future, especially quality of life and psychological problems associated with diabetes, which have not been discussed thoroughly in this paper.

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12. Appendix

1. Questionnaire - Diabetes Type 1 in children

QUESTIONNAIRE – DIABETES (T1D and T2D) IN CHILDREN: A GLOBAL PERSPECTIVE

The questionnaire is designed to gather information about children with diabetes ≤ 15 years of age. The interview is in two parts. Each part should not last more than 1 hour.

The first part is designed to map diabetes in children at a national or regional level. Each country has a number code (see list). The regions/counties/states are indicated by names. The interviewer fills out this first part of the interview based on information available on the internet and other available sources. The information will then be quality assessed with the local informant.

The second part is designed to map how children with diabetes are followed up at the local hospital/treatment centre. The interview contains multiple open, qualitative questions. The interview will therefore be tape-recorded. The tape recordings will be transcribed before the analysis takes place.

The questionnaire does not ask for personal sensitive information.

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Country (code):

Region/county/state:

Date:

Informant: name/occupation

Interview by:

PART 1

Incidence

1. The annual incidence of the different types of diabetes in this country (enter the number and percentage)
   - Type 1 diabetes (T1D)
   - Type 2 diabetes (T2D)
   - Gestational diabetes

2. The incidence of T1D and T2D among children under 15 years of age
   - The total incidence:
   - How is the distribution in the following groups of ages (estimated):
     - <5 years
     - 5-<10 years
     - 10-<15 years
     - > 15 years

3. What is the gender distribution among children with T1D and T2D in the country?

4. What are the overall proportions of the following ethnicities in this country:
   - White / European background (non-Hispanic whites)
   - Black / African background
   - Middle-East / North-African
   - Indian subcontinent
   - East-Asia
   - Middle- and South American (Hispanics)
   - Indigenous (specify)
   - Mixed (or unclassified)

5. How many children with diabetes in this country are

- White / European background (non-Hispanic whites)
- Black / African background
- Middle-East / North-African
- Indian subcontinent
- East-Asia
- Middle- and South American (Hispanics)
- Indigenous (specify)
- Mixed (or unclassified)

Prevalence

6. What is the prevalence of T1D and T2D among children in the following groups of age?
    - <5 years
    - 5-<10 years
    - 10-<15 years
    - ≥ 15 (adults)

Mortality

7. What is the average life expectancy in the country?
    - Women:
    - Men:

8. What is the average life expectancy among patients diagnosed with T1D before the age of 15?
    - Women:
    - Men:

National health

9. How many doctors per citizen? (This will differ depending on location; city, rural, town etc)

10. Is there a geographical difference in availability of doctors?

11. What is the gross domestic product (GDP) of the county?

12. What is the total expenditure on health as a percentage of the GDP?
    - Which proportion is financed by the public?
    - Which proportion is financed by private actors?

13. Which proportion of the national budget is spent on health?

14. Does the public health care system finance the costs associated with diabetes medication and equipment?
    - Yes
    - No

15. If the answer is yes on question 14, which *medication* is financed?
    - Insulin
        - Yes
            - _____% financed
        - No
    - Antidiabetic drugs
        - Yes
            - _____% financed
        - No

    Glucagon
        - Yes
          _____% financed
        - No

16. If yes on question 14, which of the following *materials* is financed
    - Syringes:
    - Needles:
    - Insulin pen:
    - Insulin pump:
    - Materials for the unconsciousness insulin pump: (needle, catheter, reservoir etc):
    - Home Blood Glucose meters:
    - Blood glucose test strips:
    - Finger-pricking devices:
    - Lancets for finger-pricking:
    - Continuous subcutaneous glucose monitoring devices:
    - Urine sticks to check for ketonuria:
    - Other:_____

17. If the answer is yes on question 14, does the patient have to pay anything? If so, how much? (%)
    - Syringes:
    - Needles:
    - Insulin pen:
    - Insulin pump:
    - Materials for the insulin pump: (needle, catheter, reservoir...):
    - Home Blood Glucose meters:
    - Blood glucose test strips:
    - Finger-pricking devices:

- Lancets for finger-pricking:
- Continuous subcutaneous glucose monitoring devices:
- Urine sticks to check for ketonuria:
- Other:_____

18. How brings the child to their check-ups?
    - Mum
    - Dad
    - Other:_____ (specify)

19. Are there any laws/public rights for parents to get extra time off work to take their children to check ups?
    - Yes
    - No

20. Are parents with chronic ill children allowed to take additional days off compared to the general population?
    - Yes (_____number of additional days)
    - No

21. Are there national guidelines for the management of children with T1D and T2D?
    - Yes
    - No

Patient organizations

22. Are there any national organizations for patients with diabetes?
    - Yes
        - For children?
        - For children and adults?
        - For adults only?
    - No

23. Are there any local organizations for patients with T1D?
    - Yes
        - For children?
        - For children and adults?
        - For adults only?
    - No

Comment:

24. What do the patient organizations offer the children and their parents?
    - Websites
    - Telephone
    - Courses
    - Information meetings
    - Holiday offers
    - Other:_____

Register for diabetes

25. Is there a national diabetes register?
    - Yes, for children
    - Yes, for adults
    - Yes, for adults and children
    - No

26. If yes, what data is registered?

Complications

27. What is the incidence of acute diabetes complications among children under 15 years of age?
    - Diabetic ketoacidosis (with hospitalization)
    - Grave hypoglycemia (unconscious with or without convulsions)

28. What is the incidence of late diabetes complications among children under 15 years of age? (estimated percentage)
    - Retinopathy
    - Nefropathy
    - Nevropathy

Country (code):

Region/county/state:

Local treatmentcenter (name and type):

Date:

Informant: name/occupation

Interview by:

PART 2

Hospitalizations and number of hospital beds

29. How many children <15 years with diabetes are admitted to hospital annually in the following wards (The total number of hospitalizations including rehospitalization)
    - Pediatric ward
    - Adolescens ward
    - Internal medical ward

30. To what age are the children managed in the pediatric wards?_____

31. If there is an adolescent department, when do the children start attending and how long can they attend there?

32. What is the maximum number of beds in the ward? _____

33. How often has the ward been full during the last 6 months? (regardless of the reason for the hospitalisation)

34. How many children with diabetes are followed up at the local hospital today?

35. How is the gender distribution among the children that are followed up at the local hospital?

36. Who takes over the responsibility for the treatment and follow-up after the diagnosis of diabetes?

- Specialist _____ (which type)
- General practitioner (GP)
- Other :_____

Diagnostics

37. Who usually make the diagnosis?
    - General practice
    - Specialised health service
    - Nurse
    - Other:_____

38. What is the average age at diagnosis?

39. What are the classical symptoms that make the patient and his or her parents contact a doctor?

40. Which diagnostic criteria have to be fulfilled to make the diagnose of diabetes?

    - International guidelines; ISPAD (Blood glucose)
    - Other guidelines:_____

41. Where are recently diagnosed juvenile diabetics treated the first time?
    - Out-patients clinic
    - Hospital ward with beds

42. If the patient is admitted to hospital, what is the average length of stay?

43. Which diagnostic criteria do you use for DKA?
    - Hyperglycemia
    - Standard Bicarbonate (< 15 mmol)
    - pH (< 7,3)
    - Urine ketons

44. What proportion of children has DKA at diagnosis?

Treatment and follow up

45. Who participates in the treatment and follow up of children with diabetes?
    - Nurse
    - Doctor
    - School nurse
    - Social worker
    - Nutritionist
    - Psychologist
    - Other:_____
    - Multidisciplinary team

46. Does the child with diabetes have one particular contact person? If yes, specify:
    - Yes:_____
    - No

47. When the diagnosis is made who is responsible for the follow-up?
    - Specialist (doctor / diabetologist)
    - Hospital doctor
    - Nurse
    - General practitioner
    - Other:_____

48. Who are educated (at the time of the diagnosis, and after discharge)?
    - The child
    - Parents
    - School
    - School nurse
    - Nursery
    - Activity leaders/coaches
    - Others:_____
    - No one

49. Does the hospital have access to interpreters when they have patients that do not speak/understand English?

50. How is the education organized?
    - Training in groups
    - Individual training
    - A combination of both

51. When is a new education organized? (re-education)

52. Is carbohydrate counting used systematically when calculating the insulin bolus in relation to food?

53. How is the education organized?

- Training in groups
- Individual training
- A combination of a and

Comment:

54. How much do parents participate in the treatment and follow up?

55. Do the adolescents get contraceptive counseling?
    - Yes (comment;)_____
    - No

56. Have you experienced unintended pregnancies in this group of patients?
    - Yes (how many? what are the characteristics of these patients; ethnicity, socioeconomic status etc?)
    - No

57. What types of treatment/treatment regimens are available for children with diabetes at the local hospital?
    - Syringes
    - Needles
    - Insulin pen
    - Insulin pump
    - Continuous Subcutaneous Glucose Monitoring
    - Others:_____
    - None

58. How many patients use multi injection (insulin > 3 times a day) therapy?

59. What proportion of the patients (in number and percentage) follow the different treatment regimens listed
    - Insulin pump:
    - Others:
    - None:?

60. Among the children under multi injection therapy what type of insulin preparations are used? (%)
    - Premixed insulin preparations
    - Intermediate-acting insulin + rapid-acting insulin
    - Analogues
        - Which combinations: _____
    - Are there any different strategies for insulin therapy concerning the child´s age?

61. Who does the patient and his or her parents contact if the child is acute ill?
    - Specialist
    - Contact person

- GP
- Emergency room
- Other:_____

Treatment goals

62. Are the ISPAD treatment goals adhered to?
    - Yes
    - No
        - If no, which guidelines are used_____

63. What are the treatment goals
    - $HbA1_c$ < 7,5 %
    - Other:_____

64. What proportions (%) of patients achieve the treatment goals?

65. How often do the children attend diabetes health check ups?_____

66. What proportions (%) of the patients attend their appointment?

    - Most patients
    - 50 %
    - Only a few

67. Who does not attend? Why? What are the characteristics of these patients?

68. Is there a screening program for autoimmune diseases?
    - Yes
    - No

69. If yes, witch diseases are included in the screening
    - Celiac disease
    - Hypothyroidism / hyperthyroidism
    - Others:_____

70. If yes, how often is the screening performed
    - At each check up
    - Annually
    - Other:_____

71. Are there any screening program concerning late diabetes complications among children with diabetes?
    - Yes
    - No

72. If yes, what kind of late diabetes complications are included in the screening program among children with diabetes? And which methods are used in the screening
    - Retinopathy:_____
    - Nephropathy;_____
    - Neuropathy:_____
    - Angiopathy:_____
    - Others:_____

73. If yes on question 70, how often is the screening performed
    - At every check up:
    - Annually:
    - Other: _____

Quality of life and mental health:

74. What assistance do the children with diabetes and their parents receive in relation to:

    - School
    - Hobbies
    - Sports

75. Are there social activities arranged for the children and their parents?

76. What kind of social activities are arranged? And who organises them?

77. Have you conducted/do you conduct research on the quality of life in the children with diabetes?

    - Yes
        - If yes, can you elaborate
    - No

78. Are intoxicants a problem among children with T1D?

- Yes
    - What kind of intoxicant?
    - What are the characteristics of these patients (gender, ethnicity, socioeconomic status etc)
- No

Comment:

Complications

79. What is the incidence (percentage) of acute diabetes complications among children with T1D under the age of 15?
    - Diabetic ketoacidosis
    - Hypoglycemic shock with unconsciousness and/or convulsions
    - Other:_____

80. What is the incidence (%) of long-term complications among children under the age of 15 years? And how old are they?
    - Retinopathy:
      How many have been treated with laser?
    - Nephropathy:
    - Neuropathy:
    - Hypertension
      How many get anti hypertension treatment?

81. What is the incidence (%) of long-term complication among adults who got the diagnose of diabetes before they turned 15 years?

    The following must be discussed:
    - How old were the patients when they where diagnosed with diabetes?
    - How many years diabetes duration at onset of the late complication?

    - Retinopathy:
    - Nephropathy:
    - Neuropathy:

82. Is overweight a problem among children with diabetes?

- If yes:
    - Are there any differences between gender, ethnicity, socioeconomic background etc?
    - In which group is the prevalence of overweight highest?
    - What kind of prevention and treatment regimens does the hospital have?
    - Are the treatment regimens effective?
    - Do children with overweight in practice have significant more complications than children with normal weight?
    - Are there other problems related to overweight and diabetes?