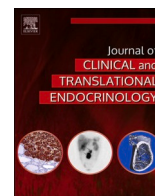


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Glycemic control and complications of type 1 diabetes among children in Tanzania

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ABSTRACT

Introduction: Knowledge on Type 1 Diabetes (T1D) in sub-Saharan Africa is scarce. This study aimed at assessing microvascular complications of Type 1 diabetes in young patients.**Method:** A retrospective study based on medical recordings from 2010–2016 was done. 604 children and young adults with T1D were recruited from five hospitals with pediatric diabetes clinics. 559 patients aged 2–35 years with known date of birth were included. Clinical data on retinopathy and neuropathy were analyzed. There was no information on renal function/ nephropathy.**Results:** Most data were missing. There was documentation on HbA1C, plasma glucose and complications in less than half of the patient files. Of those with registered HbA1c values (42.2%), 36% had HbA1c > 12.5%. There was high prevalence of retinopathy (21.5%) and neuropathy (29.4%) in spite of short mean duration of diabetes (6.2 ± 4.1 years).**Conclusion:** Many patients with T1D in Tanzania have poor metabolic control. Microvascular complications are common already after a short duration of diabetes, but the results have to be interpreted with great caution because of study limitations. Better pediatric diabetes care as well as increased awareness of diabetes is needed. Studies in resource-poor countries need careful planning, if possible with prospective design.

Introduction

Type 1 diabetes (T1D) is characterized by pronounced insulin deficiency, and therefore difficulties to get good metabolic control. Microvascular complications are closely related to metabolic control [1,2] and can to some extent therefore be prevented. The DCCT-study showed a 76% risk reduction of developing retinopathy and 34% risk reduction of developing albuminuria in patients with intensive diabetes treatment compared to the patients with conventional treatment [1]. Similarly studies have shown that lower HbA1c reduces the risk of retinopathy [3,4]. However, in spite of modern treatment the mortality is still increased [5] and life expectancy is dramatically shorter than for individuals without T1D [6]. The risk of certain cardiovascular events among patients who got T1D at <10 years of age are up to 30 times higher than for controls [6].

The prevalence of complications is much higher in sub-Saharan

Africa than in the Western world. T1D in African populations often presents with diabetic ketoacidosis (DKA) at diagnosis [7–9]. In a study at Muhimbili National Hospital in Tanzania [7], 75% of newly diagnosed children presented with DKA compared to <25% in Sweden [10]. A review of 24 studies showed a wide range in prevalence of microvascular diseases among different sub-Saharan countries. The prevalence of retinopathy ranged from 7% to 63%, neuropathy from 27% to 66% and microalbuminuria as sign of nephropathy ranged from 10% to 83% [11]. These findings might be due to higher mean HbA1c values and shortage of insulin [7,12].

With this background our study aimed at estimating the occurrence of complications in children and young adults in Tanzania. In a previous study we estimated incidence and prevalence of diabetes in a young diabetic population, in Tanzania and described their clinical manifestation including occurrence of keto-acidosis [9]. Now our aim was to estimate the prevalence of microvascular complications of what is

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considered to be Type 1 diabetes in young patients in an area where there is poor resource allocation, limited physician prioritization time, and lack of patient and provider education.

Material and methods

Study population

The study was conducted at five hospitals with pediatric diabetes clinic services in various regions of the country (Kilimanjaro Christian Medical Centre (Zonal Hospital, Northern Tanzania), Muhimbili National Hospital (National hospital in Dares Salaam), Sekou Toure Hospital (Regional hospital in Mwanza Region), Mnazi Mmoja Hospital (Main Referral Hospital in Zanzibar) and Temeke hospital (Regional hospital in Dar es Salaam). All files for children and young adults who were attending these clinics between 2010 and 2016 were reviewed. They were registered in either one of the two diabetes programs: Changing Diabetes in Children (CDIC) or International Diabetes Federation (IDF) Life For a Child Program (LFAC); sponsors of diabetes services for children with type 1 diabetes in Tanzania.

The patient population has been described earlier [9]. Thus, 604 patient files were screened and 559 patients were enrolled, 2–35 years old at the end of follow-up, in whom we had information on date of birth. Fig. 1 shows the distribution of the children in the clinics that were visited. The 559 patients are presented in Table 1, regarding characteristics including age, sex, disease duration, BMI and blood pressure, plasma glucose and HbA1c. To get a more clear picture of the different ages, very young children, children expected to be before, during and after puberty, we have divided the patients into four age groups: 0–4 years, 5–11 years (prepubertal), 12–15 years (pubertal) and > 15 years old (postpubertal). The overall female-to-male ratio was 1.1:1 and the sex distribution was similar in all age categories. The overall disease duration of diabetes was 6.2 ± 4.1 years ranging from 2.6 ± 0.7 years in the age group 0–4 years to 7.0 ± 4.1 years in the age group > 15 years. The majority of patients (73.5%) were older than 15 years (postpubertal) at the end of follow-up, with mean age in that group of 21.1 ± 3.2 years, with a few being as old as up to 34 years.

Data collection and processing

The study was a desk review where a case report form (CRF) was used to write information from the physical medical records. The variables collected included demographic data (age, sex, date of diagnosis, weight, height, blood pressure, laboratory values (any blood glucose, HbA1c) whenever available, and complications (neuropathy, defined as presence of pain, pain, hyperesthesia and /or loss of sensation to monofilament testing appearing in feet and hands) and retinopathy defined as presence of non-proliferative or proliferative diabetic

retinopathy on direct retinoscopy [13–15] while no data existed regarding renal function).

HbA1c, determined during the follow-up was available in 268 patients, more than once in 109 patients. Only 236 /559 patients had information on both mean HbA1c and date of diagnosis and thus formed the population for which Kaplan Meier estimates were calculated (See Supplementary Figures 1 and 2). In total 981 plasma glucose values were found, distributed among 365 patients. More than one value was found in 278 patients. The plasma glucose values were said to be fasting but still taken at different time-points and some might have been postprandial.

Statistical analysis

The patients were divided into four age groups; 0–< 5 years, 5–<12 years, 12–15 year and >15 years. All values are expressed as means \pm SD, medians and IQR. Kaplan Meier Survival analysis was performed on HbA1c categories (<7.5%; 58 mmol/mol; 7.5–9.9%, 58–85 mmol/mol; 10–12.5%; 86–113 mmol/mol and >12.5%, >113 mmol/mol) and age-at-diagnosis categories (<4, 5–11.5 years, 12–15 years and >15 years). The patients were followed from date of diagnosis until clinical presentation of signs suggesting neuropathy and/or retinopathy. The differences between the groups were tested using statistical log-rank test. $P < 0.05$ was considered statistically significant. SAS 9.4 was used for Kaplan Meier Survival estimates.

Results

None of the participants had hypertension (SBP > 140 mmHg, DBP > 90 mmHg) or were overweight. The overall mean blood pressure was $109 \pm 15.1/68 \pm 10.7$ and overall mean BMI was 19.4 ± 5.1 .

A total of 323 (57.8%) patients had no recordings of HbA1c. Mean HbA1c and mean fasting blood glucose are given for those where data were found between year 2010 and 2016 (Table 1). Mean HbA1c were $\geq 11\%$ for all age groups, except for the 10 patients between 0 and 4 years old who had a mean HbA1c value of $9.1 \pm 3.5\%$ (76 ± 54 mmol/mol). Thus, the majority of the children had poor glycemic control (Fig. 2). Similarly, the majority of patients had high plasma glucose (Table 1) visiting hospital. There were no registration of home blood glucose measurements.

Retinopathy and neuropathy

The overall prevalence of microvascular complications was high, with rates of 21.5% for retinopathy and 29.4% for neuropathy respectively (Table 2). However, these results have to be interpreted with great caution as the definition was soft, based on clinical symptoms and/or signs, without modern technique. Participants aged between 12 and 15

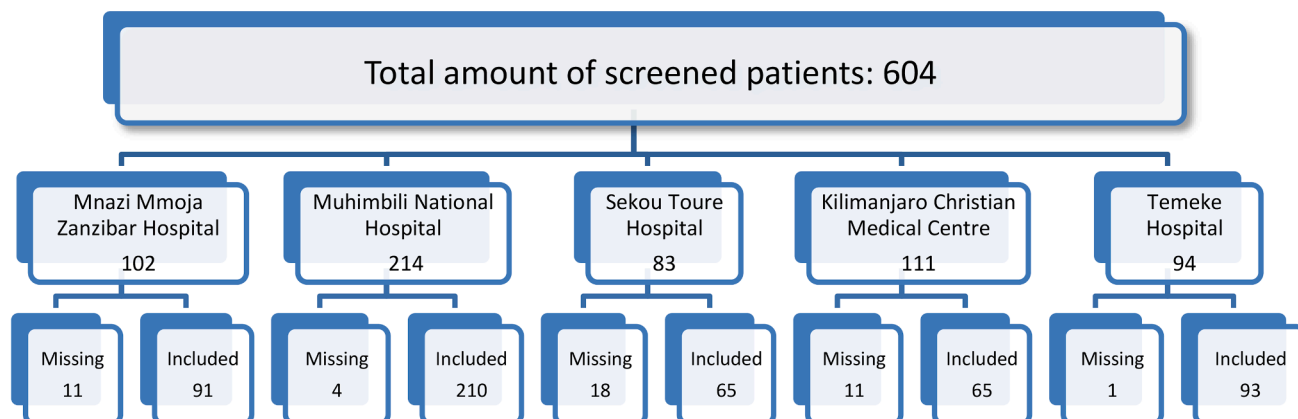


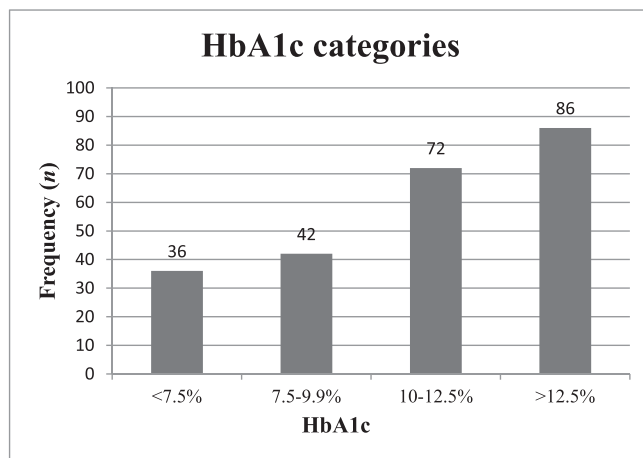
Fig. 1. Number of patients at the 5 different diabetes clinics.

Table 1

Characteristics of 559 patients followed between years 2010–2016. Percentage (%) in brackets if not otherwise mentioned.

Variables	Total n (%)	0–4 years	5–11 years	12–15 years	>15 years
Overall	559 (100)	10 (1.8)	46 (8.2)	92 (16.5)	411 (73.5)
Sex					
Male	266 (48.2)	7 (70.0)	20 (44.4)	37 (40.7)	202 (49.8)
Female	286 (51.8)	3 (30.0)	25 (55.6)	54 (59.3)	204 (50.2)
Missing	7 (1.3)	0 (0.0)	1 (2.2)	1 (1.1)	5 (1.2)
Age					
Mean (SD)	18.6 (5.4)	3.4 (0.9)	9.4 (1.8)	13.8 (1.1)	21.1 (3.2)
Median (IQR)	19.0 (15.0–22.0)	3.5 (2–4)	10.0 (8.8–11.0)	14.0 (13.0–15.0)	21.0 (18.0–23.0)
Duration of disease					
Mean (SD)	6.2 (4.1)	2.6 (0.70)	3.8 (2.6)	4.3 (2.8)	7.0 (4.1)
Median (IQR)	5.5 (3.0–8.0)	2.5 (2–3)	2.0 (2.0–5.0)	3.0 (2.0–7.0)	6.0 (4.0–9.0)
Missing	37 (6.6)	0 (0.0)	1 (2.2)	1 (1.2)	35 (8.5)
BMI					
Mean (SD)	19.4 (5.1)	17.0(2.1)	15.6 (2.8)	17 (5.0)	20.5 (4.9)
Median (IQR)	19.2 (17.1–21.9)	17.6 (15.1–18.2)	15.7 (14.7–17.0)	16.8 (15.7–18.2)	20.3 (18.5–22.7)
Missing	54 (10.7)	1 (10.0)	3 (6.5)	3 (3.3)	47 (11.4)
SBP (mmHg)					
Mean (SD)	109.0 (15.1)	91.9 (20.1)	93.4 (9.4)	104.0 (13.5)	112.4 (14.1)
Median (IQR)	109 (100.0–117.0)	90.3 (82.5–103.8)	90.5 (88.0–100.0)	102.0 (97.0–110.0)	110.5 (102.4–120.0)
Missing	129 (23.0)	2 (20.0)	10 (21.7)	21 (22.8)	95 (23.1)
DBP (mmHg)					
Mean (SD)	68.0 (10.7)	61.3 (16.5)	59.8 (9.7)	62.6 (9.49)	70.2 (10.1)
Median (IQR)	68.0 (60.7–75.0)	60.5 (52.3–64.0)	60.0 (52.0–62.0)	62.0 (58.0–70.0)	70.0 (64.0–76.0)
Missing	130 (23.3)	2 (2.0)	11 (23.9)	21 (22.8)	96 (23.4)
Fasting plasma glucose (mmol/L)					
Mean (SD)	10.0 (4.9)	11.9 (4.5)	10.2 (5.1)	9.9 (4.7)	10.0 (5.0)
Median (IQR)	9.0 (6.6–12.2)	13.8 (9.6–14.5)	10 (5.6–14.6)	8.8 (6.4–13.7)	8.8 (6.7–11.8)
Missing	232 (41.5)	4 (40.0)	19 (41.3)	37 (40.2)	172 (41.8)
HbA1c (%)					
Mean (SD)	11.1 (3.1)	9.1 (3.5)	11.4 (2.1)	11.3 (3.0)	11.0 (3.2)
Median (IQR)	11.5 (9.1–14.0)	8.2 (6.5–12.6)	11.5 (10.0–12.7)	11.1 (9.3–14.3)	11.6 (9.1–14.0)
Missing	323 (57.8)	4 (40.0)	25 (54.3)	51 (55.4)	241 (58.6)

* SD = Standard deviation, IQR = Interquartile range, SBP = Systolic blood pressure, DBP = Diastolic blood pressure.

**Fig. 2.** Frequency distribution of mean HbA1c.

years had the highest prevalence of both retinopathy (30.4%) and neuropathy (32.9%) but registration of neuropathy and/or retinopathy was found in all age groups. Thus three patients had signs of retinopathy and two of neuropathy already in the age group 0–4 years.

In an attempt to demonstrate any correlation between HbA1c as well as age at onset and retinopathy and/or neuropathy, Kaplan-Meier survival estimates were calculated. [Supplementary Figures 1 and 2](#) suggest that those diagnosed at a low age remain free from complications longer than those diagnosed as teenagers.

When comparing HbA1c and the probability of staying free from neuropathy and retinopathy after 10 years duration there was no significant difference between the HbA1c-groups ([Supplementary Figures 3 and 4](#)).

Table 2

Prevalence of retinopathy and neuropathy in the study population. Percentage (%) in brackets if not otherwise mentioned.

Variables	Total n (%)	0–4 years	5–11 years	12–15 years	>15 years
Overall	559 (100)	10 (1.8)	46 (8.2)	92 (16.5)	411 (73.5)
Retinopathy					
Yes	82 (21.5)	3 (42.9)	8 (21.6)	21 (30.4)	50 (18.7)
No	299 (78.5)	4 (57.1)	29 (78.4)	48 (69.6)	218 (81.3)
Missing	178 (31.8)	3 (30.0)	9 (19.6)	23 (25.0)	143 (34.8)
Neuropathy					
Yes	124 (29.4)	2 (25.0)	7 (16.7)	26 (32.9)	89 (30.4)
No	298 (70.6)	6 (75.0)	35 (83.3)	53 (67.1)	204 (49.6)
Missing	147 (26.3)	2 (20.0)	4 (8.7)	13 (14.1)	118 (28.7)

Discussion

The aim of this study was estimate the prevalence of microvascular complications and to investigate the association to metabolic control. We found registered signs of neuropathy and retinopathy already after very short diabetes duration, and in young children. This leads to the question whether these young children got their symptoms/signs, not as a consequence of diabetes, but at least also caused by other mechanisms. This is of course true for all ages, but especially in the very young children with these complications may have syndromal or other type of diabetes than Type 1. However, the vast majority of patients lacked registered information. One reason may be that children with T1D were not showing up on follow-up at diabetes clinics, another that measurements of HbA1c were not performed, or otherwise that registration was

never done. There were some blood glucose values, often registered as being fasting blood glucose, but it is unclear if they were fasting. Unfortunately there were no registration or comments on home blood glucose measurements which might have been used in cases when there are no HbA1c-values. A lot of missing data might to some extent be a reflection of limited resources, but even more a lack of awareness and priority among health care professionals, a problem which can be met also in rich countries with high incidence of diabetes in children [10]. As a rule even the most basal clinical information was lacking.

Thus, HbA1c was never registered in a majority of patients, but for those we have information they had overall poor glycemic control, with estimations of mean HbA1c 11.1% (98 mmol/mol) and the majority of patients had HbA1c higher than 12.5% (113 mmol/mol). These findings are consistent with those seen in other African studies [7,8]. In fact there are populations also in western countries with high mean HbA1c [16,17]. There were no differences in mean HbA1c when comparing the age categories.

A poor glycemic control among children in Tanzania probably reflects the existing limitations of diabetes care, including lack of insulin supply [12], but also lack of knowledge and motivation with inappropriate dosing of insulin, poor monitoring practices, missing insulin doses, sometimes due to eg work place and school based stigma. In contrast to developed countries where intensive diabetes treatment is offered, children in low-income countries often receive conventional insulin treatment in an inconsistent manner [18].

One serious consequence of the poor metabolic control is that prevalence of microvascular complications was high already after surprisingly short duration. Thus 21.5% had retinopathy and 29.4% were estimated to have neuropathy. These findings are similar to a previous study done on one of the sites in Tanzania and similar to what has been observed in other African countries [7,11]. However, the results in this study have to be interpreted with great caution. The registered neuropathy and retinopathy in very young children after short duration may have other cause than diabetes.

When analyzing the linkage between HbA1c and development of retinopathy and neuropathy we found no significant associations between HbA1c and complications. One explanation may be the lack of registration with no or few HbA1c values in many patients, another explanation may be the rather small groups especially with low HbA1c. However, we were able to see that patients diagnosed > 15 years of age developed neuropathy earlier in the disease course than those with onset < 15 years of age ($p = 0.03$).

There are two main lessons to learn from our study. For the first diabetes awareness and care has to be radically improved in Tanzania. Even though interpretation of our results have to be cautious we dare to conclude that diabetic complications may develop in quite young individuals already after a short duration of diabetes which will lead to enormous suffering for individuals and burden for society. Awareness of diabetes has to increase in the general population but also in health care. Health care and its authorities in Tanzania, as well as probably in many other countries, need to set up minimum standards of care in relation to their resources [19]. Registration of diagnosis based on plasma glucose and HbA1c should be self-evident even in poor countries. When the patients are diagnosed insulin and methods for self-testing have to be available and education given to the patients [20]. They should get regular visits to diabetes clinics, with basal resources for follow-up eg height and weight, plasma glucose, HbA1c, tests for albuminuria etc and the staff must register so that quality of care can be followed and improved.

The second lesson to learn from our study is how to plan studies in countries with poor resources. We tried to analyze retrospective data at clinics, which were doing their ordinary clinical work. This cannot be recommended. We certainly got a picture of the standard of clinical care, which gives arguments for the need for radical improvement. Despite poor record keeping there a bigger problem on the absence of adherence by health care providers, training dilemmas and supervision of care.

These may be complicated with the number of staff who are very few, some with knowledge on diabetes in pediatric diabetes and some without. Despite this small number of staff, these same staff still have to attend to other conditions like HIV and other infectious diseases, and cannot always be dedicated to the work with diabetes. There is shifting of patients from one place to another, and therefore the trained staff in one year's time might have shifted to other places. Among the remaining staff none has the knowledge, and the training has to restart all over.

Research in countries with lack of resources have to be well prepared and prospectively designed. There are manuals produced for developing countries, which can be of great help [15]. Collaborators at participating clinics have to be recruited and trained, studies planned and designed, with clear definition of which data should be used, so that data really are collected and registered prospectively.

Finally, donor agencies should focus on providing training along with insulin and glucose test strips, provide oversight that supplies are reaching the patients, and insist on getting information on outcomes, so that they know that donations do lead to the desired goals.

Limitations: In studies and scientific publications it is very important and relevant to point out limitations of the study. In this case we can just repeat what has been pointed out clearly and repeatedly: Data from the majority of patients are missing, and the available data are not complete and not clearly defined. Records kept are often contradictory from visit to visit. The substantial lack of data make the results very inconclusive and they have to be interpreted with considerable caution.

Ethical approval

Ethical approval was given by Muhimbili National Hospital IRB, valid for the participating hospitals, and in addition permission to conduct research was got from respective hospitals.

Author contribution

All authors have contributed significantly to the design, implementation, analysis and interpretation of the data. JL and KR conceived the study; JL, KR and EM designed the study protocol; SN and DJ carried out the clinical assessment; and all authors were involved in the analysis and interpretation of these data. EM, KR and JL drafted the manuscript; all authors critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. JL is guarantor of the paper

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcte.2020.100245>.

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