Title: Mortality amongst children and adolescents with type 1 diabetes in sub-Saharan Africa: The case study of the Changing Diabetes in Children Programme in Cameroon

Short running title: Mortality in type 1 diabetes in sub-Saharan Africa

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Abstract

Introduction

Type 1 diabetes in Africa has been associated with high mortality attributed mainly to poor insulin access. Free insulin provision programmes for people with type 1 diabetes have been introduced across Africa recently. We aimed to determine the mortality rate and associated factors in a cohort of children and adolescents with type 1 diabetes who receive free insulin treatment in sub-Saharan Africa.

Methods

We conducted a retrospective analysis using the Changing Diabetes in Children (CDiC) medical records in Cameroon between 2011 and 2015.

Results

The overall mortality rate was 33.0 per 1000 person-years (95% CI 25.2 – 43.2). Most deaths (71.7%) occurred outside of the hospital setting, and the cause of death was known only in 13/53 (24.5%). Mortality was substantially higher in CDiC participants followed up in regional clinics compared to the main urban CDiC clinic in Yaounde; 41 per 1000 years (95% CI 30.8-56.0) vs 17.5 per 1000 years (95% CI 9.4-32.5), and in those with no formal education compared to those who had some level of education; 68.0 per 1000 years (95% CI 45.1-102.2) vs 23.6 per 1000 years (95% CI 16.5-33.8). In Cox proportional multivariable analysis, urban place of care (HR=0.23, 95% CI 0.09 – 0.57; p=0.002) and formal education (HR=0.42, 95% CI 0.22 – 0.79; p=0.007) were independently associated with mortality.

Conclusion

Despite free insulin provision, mortality remains high in children and adolescents with type 1 diabetes in Cameroon and is substantially higher in rural settings and those with no formal education.

Keywords: Type 1 diabetes, mortality, Changing Diabetes in Children, Insulin access, Cameroon

Introduction

Type 1 diabetes commonly affects children and adolescents, although it can occur at any age (1). The epidemiology of the condition varies from one geographical region to another. Africa is thought to have the lowest prevalence and incidence of the disease (2). The incidence is estimated at 1.5-10 per 100 000 in sub-Saharan Africa (3). Conversely, the mortality rate associated with type 1 diabetes in sub-Saharan Africa (SSA) is historically very high, attributed mainly to poor insulin access (4, 5).

Efforts to improve insulin access over the last two decades in SSA and other resource-depleted settings have seen the birth of insulin donation schemes spearheaded by insulin-manufacturing companies (in collaboration with different charity organisations and local ministries of health) (6). For example, in 2009, Novo Nordisk launched the Changing Diabetes in Children (CDiC) programme. This programme aimed to provide comprehensive diabetes care and education, including free insulin treatment to children and adolescents with type 1 diabetes (age of onset less than 18 years) in selected countries in South-East Asia and sub-Saharan Africa (7). However, the impact of these programmes on mortality, and factors associated with mortality in the presence of free insulin provision are unknown.

The CDiC programme started in Cameroon in June 2010. Before this date, there was little available data on type 1 diabetes in children and adolescents, with many cases lost to follow-up with no concurrent medical record system or data registry (8). By December 2015, 9 clinics had been established with 535 children enrolled. Alongside insulin and equipment required for its administration, CDIC participants are also provided with glucose meters and test strips, and offered basic diabetes education at program enrolment. We, therefore, aimed to assess the impact of the CDiC programme on mortality and associated factors among a cohort of children and adolescents with type 1 diabetes in Cameroon.

Methods

Design, setting, study population, and ethical consideration

This retrospective study used the Changing Diabetes in Children (CDiC) paper-backed medical record registry system in Cameroon between 2010 and 2015. The total number of cases enrolled was 535. After verification, 18 medical records were excluded because of double entries and 517 were used for the final statistical analysis. The National CDiC coordination unit provided authorisation to use data for research purposes.

Data collection

The data collection process consisted of reviewing the medical records (from all 9 CDiC clinics in Cameroon) of the individual CDiC cases and capturing relevant data onto a pre-established extraction sheet. These included data on sociodemographic characteristics (place of care, educational profile, age at diabetes diagnosis, diabetes duration, age at enrolment, glycaemic control, presence or absence of chronic complications and vital status). Glycaemic control (HbA1c) was retrieved from the medical records at two time points; at CDiC enrolment and the last follow-up visit. We also retrieved information on the presence or absence of chronic complications (neuropathy, retinopathy, nephropathy, and diabetes foot) at entry into the CDiC programme. CDiC clinicians assessed these as part of their continuum of care. In addition, data on the cause and place of death were recorded where applicable. The cause of death was obtained from the medical records of the deceased CDiC participants.

Statistical analysis

The mortality rate was determined by reporting the number of deaths to the number of cases followed up during the study period. The duration of follow-up was calculated from the date of enrolment into

the programme until the censoring date (December 31, 2015) or date of death. Cox proportional hazard models were used to examine factors associated with mortality.

Results

Baseline sociodemographic and clinical characteristics of the study population

Table 1 shows the characteristics of the CDiC participants at baseline and at follow up for the whole group and split by survivors and non-survivors. The proportion of males was 53.2%. The median (interquartile) age at diabetes diagnosis and duration of diabetes at death or censoring were 15.0 (12.5-17.1) years and 4.0 (2.3-6.0) years, respectively. The median duration of diabetes at enrolment into the CDiC programme was 0.24 (0.03-2.09) years. The median HbA1c at entry into the CDiC programme and last recorded follow-up visit was 11.5% (8.5-14.0) and 9.6% (7.5-13.4). Thirty-one participants (6.0%) were reported to have at least one chronic complication at CDiC enrolment.

Clinic location or place of care out of Yaounde (meaning at a regional CDiC clinic) and lack of formal education were significantly more common in those who died (non-survivors), with no differences seen for the other factors examined such as sex, age at diabetes diagnosis, and presence of complications.

Mortality rate, place and causes of death

Overall, 53 deaths (10.3%) were recorded over the follow-up period. The median (interquartile) follow-up period of the CDiC participants at death or censoring was 3.3 (2.0-4.3) years. The overall mortality rate was 33.0 per 1000 person-years (95% CI 25.2-43.2). Mortality was substantially higher in CDiC participants followed up in regional clinics compared to the main urban CDiC clinic in Yaounde; 41 per 1000 person-years (95% CI 30.8-56.0) vs 17.5 per 1000 person-years (95% CI 9.4-32.5). CDiC participants with no formal education had higher mortality rates than those with some level of education; 68.0 per 1000 person-years (95% CI 45.1-102.2) vs 23.6 per 1000 person-years (95% CI 16.5-33.8). Most deaths (71.7%) occurred outside the hospital setting, and the cause of death was known only in 24.5% (13/53) of cases. The known causes of death were chronic kidney disease in 2 participants, chronic liver disease in 1 participant, hypoglycaemia in 1 participant, infection in 3 participants and diabetic ketoacidosis in 6 participants.

Factors associated with mortality

Table 2 shows the factors associated with mortality using the Cox proportional hazard models. In Univariate analysis, only place of care and education level were associated with mortality. In multivariable analysis, with additional adjustment for age at diabetes diagnosis and sex, the urban place of care vs rural (HR=0.23, 95% CI 0.09 – 0.0.57; p=0.002) and formal education vs no formal education (HR=0.42, 95% CI 0.22 – 0.79; p=0.007) were both independently associated with mortality.

Discussion

Our study showed that the crude mortality estimate in the Changing Diabetes in Children programme over the follow-up period was 30.0 per 1000 person-years. Furthermore, the place of care (clinic location) and educational profile were strongly and independently associated with mortality. These findings suggest that mortality in type 1 diabetes remains substantially high compared to that seen in developed countries despite free insulin provision and that mortality is strongly associated with the clinical care setting and education. These findings also underscore marked inequalities that need to be addressed to provide equitable healthcare services for children and adolescents with diabetes in sub-Saharan Africa.

Limitations of this study include that we had limited information on the baseline characteristics of the CDiC participants, with a lack of formal assessment of factors like social status and diabetes education, meaning that potentially important predictors of mortality could not be examined. A further limitation is that the cause of death was not available for the majority of the participants, limiting our understanding of the different aetiologies of death.

However, the mortality estimate in our study is lower than many previous studies conducted before free insulin provision programmes in Africa (9, 10). Historical data suggests that mortality linked with type 1 diabetes was as high as 80% in many African countries in the 1990s before the advent of these programmes (5). This situation would be similar to that seen in the pre-insulin era in the western world. However, type 1 diabetes mortality remains substantially higher in sub-Saharan African countries than in developed countries (11)(12). In Rwanda's Life for a Child (LFAC) programme, the mortality rate was 13.9 per 1000 person-years between 2009 and 2011 (10). Though lower than our mortality estimate, this figure remains substantially high compared to that seen in high-income countries (13-15). In our study, the cause of death was unexplained in three-quarters of the cases. This may be because almost all unexplained death cases occurred out of the hospital, meaning they probably died at home from diabetes-related causes. This suggests a need to educate parents of children and adolescents with diabetes to seek proper and adequate care when experiencing illness.

Our study showed that the overall glycaemic control of the CDiC participants improved from the time of enrolment to the last recorded follow-up visit. Overall glycaemic improvement has previously been reported in CDiC and similar programmes across Africa (8, 16). Although there was an overall improvement in the glycaemic control in our study, mortality was still very high, suggesting that other factors may drive mortality. Also, the median age of onset of diabetes in our study was 15 (12-17) years. This is higher than reported in many Caucasian studies but similar to other African studies (17, 18). Some authors have suggested that a later age of onset seen in sub-Saharan Africa may be because younger-aged children are most likely to die due to misdiagnosis.

Mortality was higher in CDiC participants with no formal education and those followed up at a regional CDiC clinic. Regional CDiC clinics primarily serve rural settings as opposed to the main CDiC clinic in Yaounde. The CDiC clinic in Yaounde serves as the central coordination hub for the CDiC programme in Cameroon. Yaounde is the capital city of Cameroon and arguably has a higher aggregate density of social and healthcare amenities than the other regions of the country (19). Access to healthcare and social support systems is generally better in urban than in rural settings in sub-Saharan Africa (20). The main urban CDiC clinic in Yaounde is staffed by dedicated nurses, dieticians, specialist diabetologists, and paediatric endocrinologists. In contrast, the regional CDiC clinics are staffed mainly by nurses and are less well resourced, without access to the same level of care. Paediatric diabetes care is generally best offered by a multi-disciplinary team comprising a Paediatric Endocrinologist, a diabetes nurse educator and a dietician according to the International Society for Paediatric and Adolescent Diabetes (ISPAD) guidelines (21). However, many sub-Saharan African countries, including Cameroon, may not have adequate human resources to implement the ISPAD guidelines for many years to come. Thus, care might likely be further improved by focusing on the effective redistribution of trained healthcare workers and on ongoing education of staff, patients, and families. Our results suggest that targeting these efforts towards rural clinics and CDiC participants without formal education will be particularly important to improve outcomes for those at the highest mortality risk.

Conclusion

Despite free insulin provision, mortality remains high in children and adolescents with type 1 diabetes in Cameroon and is substantially higher in rural settings and those with no formal education.

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Table 1: Table showing the characteristics between survivors and non-survivors in the CDiC programme in Cameroon.

Characteristics	Survivors (n=464)	Non-survivors (n=53)	P Value
Baseline Characteristics			
Sex – Male, n (%)	251 (54.1)	24 (45.3)	0.22
Clinic Location - Out of Yaounde, n (%)	294 (63.4)	43 (81.1)	0.01
Educational profile – Received formal education, n (%)	340 (73.3)	30 (56.6)	0.01
Age at diabetes onset (years)	15.1 (12.5-17.3)	13.5 (10.8-15.2)	0.66
At least 1 chronic complication, n (%)	27 (5.8)	4 (7.5)	0.62
At CDiC Enrolment			
Age at entry into programme (years)	16.7 (14.4-18.1)	15.6 (13.7-17.6)	0.41
Duration of diabetes at entry into programme (years)	0.23 (0.03-2.09)	0.59 (0.04-2.00)	0.57
HbA1c at entry into programme, (%)	11.5 (8.5-14.0)	11.4 (7.6-14.0)	0.54
HbA1c at last follow-up visit, (%)	9.7 (7.6-13.4)	8.8 (6.1-11.8)	0.28
Follow-up Characteristics			
Age at death (years)	//	18.2 (16.0-20.8)	//
Overall diabetes duration (years)	4.1 (2.4-6.0)	3.1 (1.1-4.6)	//
Duration of diabetes within the CDiC programme (years)	3.5 (2.1-4.3)	2.1 (0.7-3.0)	//

Results are presented in frequency (percentage) and median (interquartile ranges). CDiC: Changing Diabetes in Children, HbA1c: Glycated haemoglobin.

Table 2: Cox regression analysis showing factors associated with mortality in the CDiC programme in Cameroon

Characteristics	Hazard Ratio	95% CI	P-Value
Univariable Model			
Sex	0.74	0.42 – 1.26	0.27
Age at diabetes diagnosis	1.02	0.94 – 1.11	0.58
Age at entry into the CDiC programme	0.99	0.89 – 1.12	0.96
Duration of diabetes at entry into the CDiC programme	0.98	0.87 – 1.09	0.71
HbA1c at entry into the CDiC programme	0.94	0.84 – 1.07	0.39
HbA1c at last recorded visit	0.92	0.78 – 1.07	0.29
Presence of complications	1.05	0.37 – 2.92	0.92
Educational profile	0.37	0.22 – 0.66	0.001
Clinic location	0.41	0.20 – 0.82	0.01
Multivariable Model			
Sex	0.87	0.47 – 1.59	0.65
Age at diabetes diagnosis	0.99	0.92 – 1.07	0.94
Educational profile	0.42	0.22 – 0.79	0.007
Clinic location	0.23	0.09 – 0.57	0.002

CDiC: Changing Diabetes in Children, HbA1c: Glycated haemoglobin.