ISPAD-JDRF Research Fellowship Report

Project Title: Multi-ethnic Analysis of Biomarker-Defined Type 1 Diabetes in the Young (MADDY) Study

Jean Claude Katte. MD, PhD (Type 1 Diabetes in sub-Saharan Africa)

ISPAD Membership: 72509208

National Obesity Centre and the Endocrinology and Metabolic Diseases Unit, Yaounde Central Hospital, Yaounde, Cameroon

Department of Clinical and Biomedical Sciences, University of Exeter Medical School, Exeter, United Kingdom.

Mentor: Professor Eugene Sobngwi

National Obesity Centre and the Endocrinology and Metabolic Diseases Unit, Yaounde Central Hospital, Yaounde, Cameroon.

Department of Internal Medicine and Specialities, Faculty of Medicine and Biomedical Sciences, University of Yaounde 1, Yaounde, Cameroon.

Co-Mentor: Dr Mesmin Y. Dehayem

National Obesity Centre and the Endocrinology and Metabolic Diseases Unit, Yaounde Central Hospital, Yaounde, Cameroon.

Department of Internal Medicine and Specialities, Faculty of Medicine and Biomedical Sciences, University of Yaounde 1, Yaounde, Cameroon.

1.Background

The definition, pathogenesis, and genetics of type 1 diabetes.

Type 1 diabetes is a chronic multifactorial disease characterised by the absolute deficiency of insulin due to the autoimmune destruction of the beta cells of islet of Langerhans in the pancreas in persons with increased genetic disease susceptibility (1). Circulating autoantibodies to different islet cell antigens following the destruction of the beta cells are usually detectable in blood (2). Genetic factors also contribute to the pathogenesis of T1D and approximately 95% of patients presents polymorphisms of the class II Human Leucocyte antigen (HLA) genes. The HLA complex however provides the greatest contribution to the overall genetic susceptibility (3). Apart from HLA genes, over 50 different loci have also been associated with the susceptibility to T1D through genome-wide association studies though no single gene is either necessary or sufficient to predict the development of T1D (3, 4).

Is Type 1 diabetes in sub-Saharan Africa the same has Type 1 diabetes elsewhere?

Type 1 diabetes has been poorly characterised, with very sparse information available in the literature about the characteristics of the disease in Africa (5). Atypical young onset diabetes is often reported by clinicians in sub-Saharan Africa, including patients who have the phenotype of type 1 diabetes but do not appear to have an absolute insulin requirement (6). The onset of T1D in many SSA populations seem to occur at later ages (20s to 40s) than what is generally seen in Caucasian populations (7). The age of onset of the disease and lower rates of autoimmunity in some African studies seem to suggest that there may be a difference in both the autoimmune and genetic underpinnings of type 1 diabetes between African and Caucasian populations (8, 9, 10). However, some of the studies done have been limited by their small sample sizes, use of non-standardised immunological methodologies, and limited geographic representation (5). Therefore, whether type 1 diabetes is different in African populations than what has been described elsewhere cannot be ascertained.

Significance of this research project

Type 1 diabetes in sub-Saharan Africa is understudied despite the growing numbers of individuals diagnosed as having the condition in the African continent (11). Furthermore, the condition has been associated with high early mortality within the first few years following diagnosis largely attributed to poor insulin access and misdiagnosis (12). Understanding the true phenotype and pathogenesis of type 1 diabetes in sub-Saharan Africa is critical improving our depth of knowledge about the best ways to treat to prevent the early mortality. Some pilot data from our research collaboration conducted in Cameroon and Uganda as part of the Young-Onset Diabetes in sub-Saharan Africa (YODA) study revealed about 70% of children and young adults diagnosed with T1D have islet autoantibody-negative diabetes, with substantially lower T1D genetic risk scores compared to those with true autoimmune diabetes (13). While the findings from this study suggested that other forms of diabetes may be predominant amongst those diagnosed as having type 1 diabetes in Cameroon and Africa, the results also shows that classical autoimmune type 1 diabetes is present. This current study seeks to focus on the individuals with true autoimmune type 1 diabetes by succinctly describing their clinical and genetic phenotype in comparison with individuals with type 1 diabetes in a white Caucasian population.

2. Research question, key aims and objectives.

Research question: Are the clinical features and markers of genetic susceptibility similar in between children and young adults with true autoimmune type 1 diabetes from sub-Saharan Africa and a white Caucasian population?

Aim: To describe the phenotype and assess for markers of type 1 diabetes aetiology in individuals with biomarker-defined type 1 diabetes from sub-Saharan Africa and compare with individuals with autoimmune type 1 diabetes of white ancestry.

Aim 1: To determine the clinical and biochemical features of African individuals with biomarker-defined type 1 diabetes and compare with individuals with type 1 diabetes of white ancestry.

Aim 2: To assess for type 1 diabetes genetic susceptibility using the T1DGRS within the group of individuals with biomarker-defined type 1 diabetes from SSA and compare with individuals with type 1 diabetes of white ancestry.

3. Project Plan

African Cohort: YODA Dataset This study will leverage the Young-Onset Diabetes in sub-Saharan Africa (YODA) study dataset. In 2018 to 2022, I set up and completed the YODA study to investigate the apparent type 1 diabetes occurring in children and young adults in SSA. The YODA study recruited 644 participants from Cameroon and Uganda with detailed clinical and biological assessment age, sex, age at diabetes onset, baseline anthropometric parameters including BMI, islet autoantibodies, C-peptide, and array genotyping data on the Global Sequence Array (GSA). With the help of collaborators from Tanzania and South Africa, we have now completed the recruitment of 290 and 442 children and young adults.

White Ancestry Cohort: UNITED Study: The UNITED study was a population-based study that recruited individuals aged below 50 years, diagnosed with diabetes before the age of 30 years. Amongst the 1875 recruited within the UNITED Study. I will select those with a clinician diagnosis of type 1 diabetes diagnosed before the age of 30 years with at least one islet autoantibody present to match the same criteria used within the YODA study.

Biomarker defined type 1 diabetes: Biomarker defined type 1 diabetes within the African cohorts will be defined as children and adolescents with a clinical diagnosis of type 1 diabetes with at least a single positive islet autoantibody result. The islet autoantibody tested are the glutamic acid decarboxylase (GAD65), islet antigen 2 (IA2) and zinc transporter 8 (ZnT8). Plasma C-peptide will be used to define severe insulin deficiency. Severe insulin deficiency will be defined as post meal plasma C-peptide.

Generation of the type 1 diabetes genetic risk score: To examine for genetic susceptibility to type 1 diabetes, I will calculate a type 1 diabetes genetic risk score (T1DGRS) from common genetic variants associated with type 1 diabetes using the 67 SNPs (with 14 SNPs and 53 SNPs tagging the HLA and non-HLA loci) described by Sharp and colleagues (14). This T1DGRS has been shown to have utility across a range of ethnicities.

Statistical analysis: Firstly, I will identify the individuals with true autoimmune type 1 diabetes within the different YODA cohorts (Cameroon, Uganda, Tanzania, South Africa) by the presence of at least one islet autoantibody being positive. To demonstrate that individuals with

a clinical diagnosis of type 1 diabetes are different from those with true autoimmune type 1 diabetes within the African cohorts, I will compare key clinical features (age at diabetes onset, BMI, C-peptide levels) and the T1DGRS across both groups. To examine the similarities in clinical features and genetic susceptibility between individuals with true autoimmune diabetes within the African YODA Cohort and White Caucasians within the UNITED study, I will compare the age of diabetes onset, BMI, C-peptide levels, total combined insulin dose and the T1DGRS across both groups. The analysis will be adjusted for duration of diabetes where necessary.

4.Current Status of First Six Months (January – June 2024)

Ethical approval for this study were already in place in the different countries; Cameroon 2377/CE/CNERSH/SP; Uganda HS 2762; Tanzania NIMR/HQ/R.8a/Vol.IX/3548 and South Africa M200174. I have now completed:

- Data collection and collation of the datasets in all the 4 African cohorts (Cameroon, Uganda, Tanzania, and South Africa).
- Summary of the key routine clinical and biological features of the African cohorts.
- Calculated the genetic susceptibility to type 1 diabetes using the 67 single nucleotide polymorphism (SNPs) genetic risk score in all the African cohorts.

Table 1 below shows the clinical and biological characteristics of the participants that have been enrolled into the different African country cohorts.

5.Next steps

The next steps in this research:

- Continue data cleaning exercise of the African cohorts.
- Analyse the African data for key clinical and biological components based on biomarker definition of type 1 diabetes (all participants presenting with ≥1 islet autoantibody positivity).
- Complete access to European dataset of individuals with known type 1 diabetes.
- Compare data of participants with biomarker-defined type 1 diabetes from Africa to those with type 1 diabetes from European population.
- Write a manuscript in view of publication in a peer-reviewed scientific journal.

References

1. Thomas NJ, Jones SE, Weedon MN, Shields BM, Oram RA, Hattersley AT. Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. Lancet Diabetes Endocrinol. 2018;6(2):122-9.

2. Regnell SE, Lernmark A. Early prediction of autoimmune (type 1) diabetes. Diabetologia. 2017;60(8):1370-81.

3. Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. Lancet. 2001;358(9277):221-9.

4. Redondo MJ, Steck AK, Pugliese A. Genetics of type 1 diabetes. Pediatr Diabetes. 2018;19(3):346- 53.

5. Katte JC, McDonald TJ, Sobngwi E, Jones AG. The phenotype of type 1 diabetes in sub-Saharan Africa. Front Public Health. 2023;11:1014626.

6. Padoa CJ. The epidemiology and pathogenesis of type 1 diabetes mellitus in Africa. Journal of Endocrinology, Metabolism and Diabetes of South Africa. 2011 Dec 1;16(3):130–6.

7. Gill GV, Mbanya J-C, Ramaiya KL, Tesfaye S. A sub-Saharan African perspective of diabetes. Diabetologia. 2009 Jan;52(1):8–16.

8. Kalk WJ, Huddle KR, Raal FJ. The age of onset and sex distribution of insulin-dependent diabetes mellitus in Africans in South Africa. Postgrad Med J. 1993;69(813):552-6.

9. Padoa CJ, Rheeder P, Pirie FJ, Motala AA, van Dyk JC, Crowther NJ. Identification of a subgroup of black South Africans with type 1 diabetes who are older at diagnosis but have lower levels of glutamic acid decarboxylase and islet antigen 2 autoantibodies. Diabet Med. 2020;37(12):2067-74.

10. Asanghanwa M, Gorus FK, Weets I, der Auwera BV, Aminkeng F, Mbunwe E, et al. Clinical and biological characteristics of diabetic patients under age 40 in Cameroon: relation to autoantibody status and comparison with Belgian patients. Diabetes Res Clin Pract. 2014;103(1):97-105.

11. International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: 2021. Available at: https://www.diabetesatlas.org.

12. Makame MH. Childhood diabetes, insulin, and Africa. DERI (Diabetes Epidemiology Research International) Study Group. Diabet Med. 1992;9(6):571-3.

13. Katte JC, Sobngwi, E, Dehayem, MY, Deshmukh, S, Patel, K , Shields, B, ; Hattersley, AT, McDonald, TJ, Jones, AG. Evidence of atypical non-autoimmune diabetes amongst young people diagnosed with type 1 diabetes in Cameroon: results from young-onset diabetes in sub-Saharan Africa study. Diabetologia. 2022;65(SUPP 1):S208-S.

14. Sharp SA, Rich SS, Wood AR, Jones SE, Beaumont RN, Harrison JW, et al. Development and Standardization of an Improved Type 1 Diabetes Genetic Risk Score for Use in Newborn Screening and Incident Diagnosis. Diabetes Care. 2019;42(2):200-7.

Table 1: Clinical and biological characteristics of the participants

Characteristics	Cameroon	Uganda	Tanzania	South Africa
Sample number	**312**	**394**	**291**	**340**
Sex – Male, n (%)	168 (53.8)	182 (46.2)	140 (48.1)	154 (45.3)
Family history of diabetes, n (%)	29 (9.4)	31 (7.9)	34 (11.7)	83 (24.5)
Age at diagnosis, years	15 (5)	15 (6)	13 (6)	17 (7)
Diabetes duration, years	5 (4)	7 (5)	5 (4)	8 (7)
Total insulin dose, IU/day	53 (28)	42 (16)	35 (14)	NA
Weight, kg	59.1 (15.8)	55.8 (14.0)	49.8 (16.0)	65.6 (18.7)
BMI, kg/m^2	22.4 (8.7)	22.8 (15.7)	20.8 (5.2)	24.9 (6.0)
HbA1c, mmol/mol	88 (33)	92 (36)	NA	92 (32)
Plasma C-peptide, pmol/L	195 (302)	248 (412)	226 (646)	146 (224)
Severe insulin deficiency*, n (%)	226 (72.2)	256 (65.1)	150 (73.9)	170 (74.9)
T1DGRS	9.37 (2.59)	10.23 (2.61)	10.58 (2.78)	10.69 (2.56)

Data are in mean (standard deviation) and frequency (percentage). NA: Not available. * Denotes severe insulin deficiency meaning plasma C-peptide <200 pmol/L.