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RESEARCH ARTICLE

Acute phase ketosis-prone atypical diabetes is associated with a pro-inflammatory profile: a case-control study in a sub-Saharan African population

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Abstract

Background It is unknown whether inflammation plays a role in metabolic dysfunction on ketosis-prone diabetes (KPD). We aimed to assess the inflammatory profile in sub-Saharan African patients with KPD during the acute ketotic phase as well as during non-ketotic hyperglycemic crises.

Methods We studied 72 patients with non-autoimmune diabetes: 23 with type 2 diabetes mellitus (T2D), and 49 with KPD, all admitted in hyperglycemic crisis (plasma glucose ≥250 mg/dl). The T2D and KPD groups were matched by sex, age, and Body Mass Index. KPD was sub-classified into new-onset ketotic phase ($n = 34$) or non-ketotic phase ($n = 15$). We measured TNF-α, MCP-1, MIP1-α, IL-8, MIP1-β, and VEGF in the serum of all participants.

Results TNF-α and IL-8 were higher in participants with KPD compared to those with T2D ($p = 0.02$ TNF-α; $p = 0.03$ IL-8). TNF-α and IL-8 were also higher in the ketotic phase KPD group compared to the T2D group ($p = 0.03$ TNF-α; $p < 0.001$ IL-8) while MIP1-α was lower in people with ketotic phase KPD compared to their T2D counterparts ($p = 0.03$). MIP1-α was lower in the ketotic phase KPD group compared to the non-ketotic phase KPD group ($p = 0.04$). MCP-1 was lower in non-ketotic phase KPD compared to T2D ($p = 0.04$), and IL-8 was higher in non-ketotic phase KPD compared to T2D ($p = 0.02$).

Conclusions Participants with KPD had elevated pro-inflammatory cytokines compared to their T2D counterparts. Ketotic phase KPD is associated with a different pro-inflammatory profile compared to non-ketotic phase KPD, and the inflammatory profile appears to be comparable between non-ketotic phase KPD and T2D patients.

Keywords Ketosis-prone diabetes · Type 2 diabetes · Inflammation · Sub-Saharan Africa

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Background

Insulin resistance and relative pancreatic β-cell failure are the two key concurrent events of type 2 diabetes mellitus (T2D) [1]. Among the factors involved in the pathophysiology of T2D, inflammation was highlighted as playing a leading role [2–5]. There is increasing evidence that insulin secretion deficiency and insulin resistance are associated with low-grade inflammation in T2D [6–8]. Ketosis prone diabetes (KPD), described early in the 1960s, is nowadays recognized as a T2D phenotype (although classified by the American Diabetes Association (ADA) as type 1B diabetes). The onset characteristics are ketosis or ketoacidosis, insulin requirement as in type 1 diabetes, but absence of antibody mediated autoimmunity. After the initial acute insulin deficiency, 50–75% people with KPD will experience a remission, defined as the recovery of β-cell function with the possibility of withdrawing insulin treatment while maintaining excellent glycemic control only with a balanced diet and/or oral hypoglycemic drugs [9, 10].

Although people with KPD display clinical features of type 1 diabetics at diabetes onset, previous studies revealed that KPD phenotype in the follow-up is much closer to T2D. In fact, KPD in near-normoglycemic remission displayed muscle, adipose tissue and hepatic insulin resistance, residual insulin secretion, as well as inappropriate glucagon secretion [11–13]. KPD is associated with an acute, reversible dysfunction of β-cell function [14, 15]. There is no evidence of association between DRB1 DQB1 genetic profile susceptibility in people with KPD [16]. Until now, the underlying mechanism of KPD phenotype is still unclear [15]. Genetic factors implicated in insulin secretion, β-cell differentiation, and protection against oxidative stress may contribute to the disease onset. However none of these approach could identify the individual factors underlying the phenomenon of acute insulin secretion deficit with later on during remission, recovery of β-cell function in people with KPD phenotype [15, 17–21]. Investigating metabolic dysregulation in people with KPD could be a promising strategy toward understanding diabetes phenotype [15].

Moreover, it is unknown whether inflammation may play a role in metabolic dysfunction as it does in T2D [2–5]. Brooks-Worrell et al. reported that islet-specific-T-cell response was strong and percentages of pro-inflammatory CD14+ and CD16+ monocytes were higher in KPD participants with altered β-cell function as opposed to those with preserved β-cell function [22]. However, the design of this study did not distinguish between people with KPD at ketotic onset from those with KPD in the non-ketotic phase. In this study, we focused on the inflammatory profile of KPD in the acute ketotic phase from those in the non-ketotic phase and T2D patients. The purpose of this study is to identify whether acute ketotic phase is associated with a specific inflammatory profile that may explain the KPD phenotype. We investigated the inflammatory profile in a sub-Saharan African population with non-autoimmune diabetes.

Methods

Setting

This study was conducted between November 2014 and February 2015 at the National Obesity Center of Yaoundé Central Hospital, a reference center for diabetes care that has the largest pool of people with diabetes in the capital city of Cameroon. Ethical clearance was approved by the National Ethics Committee of Cameroon. All those taking part provided written informed consent.

Participants

The study population has been described previously [23]. We enrolled a total of 72 people with non-autoimmune diabetes (30 M / 42 F, 55 ± 13 years, BMI 27.7 ± 13.4 kg/m^2) in a hyperglycaemic crisis with a fasting plasma glucose ≥13.9 mmol/l (250 mg/dl), including people with T2D (n = 23, 10 M / 13 F, 57 ± 13 years, BMI 27.7 ± 15.5 kg/m^2) and KPD (n = 49, 20 M / 29 F, 51 ± 12 years, BMI 27.7 ± 5.8 kg/m^2). All participants fasted for an average of 10 h. People with T2D and KPD were matched by sex, age, and BMI. KPD was defined as new-onset diabetes without precipitating events such as infection, stress, or corticotherapy, with significant ketosis (urine ketones ≥13.7 mmol/l (80 mg/dl) requiring initial insulin treatment to achieve glucose control in the absence of cytoplasmic islet cell autoantibodies and glutamate decarboxylase 65 kDa autoantibodies [9, 13].

For the purposes of this study, KPD was further subclassified as newly diagnosed ketotic phase (n = 34, 17 M / 17 F, 50 ± 12 years, BMI 26.0 ± 4.5 kg/m^2) in the case of a first acute episode or, as non-ketotic phase (n = 15, 3 M / 12 F, 53 ± 11 years, BMI 31.4 ± 6.6 kg/m^2) for people who previously had ketotic phase KPD and were experiencing a hyperglycaemic crisis after initial remission without ketosis at inclusion in this study. This distinction was made using hospital records along with the confirmation by their primary care physicians.

T2D was defined as previously established diabetes managed by lifestyle measures or oral hypoglycaemic medications, without episode of ketosis and in the absence of cytoplasmic islet cell autoantibodies and glutamate decarboxylase 65 kDa autoantibodies [9, 13].

People with known history of maturity-onset diabetes, endocrinopathies, pancreatic disease, and autoimmune type 1 diabetes and insulin treatment (including oral glucose dependent insulin secretor treatment) were not included in the study.

All those enrolled in the study underwent a physical examination and further investigation to rule out potential precipitating events. Blood samples were collected at time of hospitalization for biological assessment of diabetes-associated antibodies, fasting blood glucose, HbA1c, and inflammatory biomarkers. Urine samples were collected to assess urine ketones.

Biochemical analysis

As previously described [24], all the assays were performed twice. The concentration of plasma glucose was measured using the hexokinase method (Roche Diagnostics, Mannheim, Germany). Immunofluorescence methods were used to anlysed cytoplasmic islet cell titres on group O donor pancreas sections by comparing consecutive dilutions of the testing serum with the Juvenile Diabetes Foundation standard curve. The radioligand binding immunoassay was used to measured glutamate decarboxylase 65 autoantibodies using their respective radiolabeled recombinant antigen molecules (CIS Bio International). HbA1c levels were determined form whole blood at the time of collection using the HLC-723G7 automatic HbA1c analyser (Tosoh Corp., Tokyo, Japan).

Biomarker profile analysis

To measure the serum levels of Tumor necrosis factor alpha (TNF-α), Monocyte Chemoattractant Protein-1 (MCP-1), Macrophage inflammatory protein one alpha (MIP1-α), Interleukin-8 (IL-8), Macrophage inflammatory protein one beta (MIP1-β), and Vascular endothelial growth factor (VEGF), a multiplex bead analysis system was used (Milliplex X-MAP, EMD Millipore Corp, Billerica, MA). This was done using samples of 25 μL. The coefficient of variation was, respectively, <15% for intra-assay and < 18% for inter-assay. The Luminex 100 instrument (Luminex, Austin, TX) was used to measure the specific fluorescence of each biomarker after an overnight incubation in 96 well plates. Logistic regression-generated standard curves was used for the quantification together with the reference cytokine standards. All the biomarker concentrations were given a zero when they were below the lowest concentration point in the standard curves [25].

Statistical analysis

Data was processed and analyzed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). Results are presented as counts with percentages and medians with interquartile range (IQR). We used the Fisher's exact test to compare categorical variables. The nonparametric Mann Whitney U-test and Kruskall-Wallis test were used to compare continuous variables between study groups**.** Differences were considered statistically significant at p value <0.05.

Availability of data and material The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Results

Data on sociodemographic information, medical history, metabolic characteristics (insulin secretion as well insulin resistance measured by HOMA-β and HOMA-IR respectively) have been described previously [24]. We included 72 people with non-autoimmune diabetes (30 M / 42 F, 55 ± 13 years, BMI 27.7 ± 13.4 kg/m^2), including people with T2D (n = 23, 10 M / 13 F, 57 ± 13 years, BMI 27.7 ± 15.5 kg/m^2) and those with KPD (n = 49, 20 M / 29 F, 51 ± 12 years, BMI 27.7 ± 5.8 kg/m^2). Among the 49 people with KPD, 34 (69.4%) were in ketotic phase (n = 34, 17 M / 17 F, 50 ± 12 years, BMI 26.0 ± 4.5 kg/m^2) and 15 (30.6%) were in non-ketotic phase (n = 15, 3 M / 12 F, 53 ± 11 years, BMI 31.4 ± 6.6 kg/m^2).

Inflammatory profile in diabetes phenotype

Comparison between people with ketosis-prone diabetes and people with type 2 diabetes

TNF-α and IL-8 were higher in people with KPD than in those with T2D [median 15.4 (IQR 9.5–19.7) pg/ml vs. 9.9 (7.7–14.0) pg/ml, (p = 0.02) for TNF-α, and median 32.6 (IQR 10.9–114.4) pg/ml vs. 9.5 (4.8–22.5) pg/ml, (p = 0.03) for IL-8].

No significant difference was observed for MCP-1, MIP1-α, MIP1-β, and VEGF between the two groups (p > 0.05) (Table 1).

Comparison between people in ketotic phase ketosis-prone diabetes, non-ketotic phase ketosis-prone diabetes and those with type 2 diabetes.

Tumor necrosis factor alpha

TNF-α was significantly higher in people in ketotic phase KPD than in those with T2D [median 17.4 (IQR 9.5–20.3) pg/ml vs. 9.9 (7.7–14.0) pg/ml, (p = 0.03)]. TNF-α was comparable between non-ketotic phase KPD and T2D groups, as well as between non-ketotic phase KPD and ketotic phase KPD groups (Fig. 1a).

Table 1 Inflammatory profile in type 2 diabetes and ketosis-prone diabetes participants

Variables (pg/ml)	T2D ($n = 23$)	KPD ($n = 49$)	p-value
TNF-α	9.9 (7.7–14.0)	15.4 (9.5–19.7)	0.02
MCP-1	276.9 (251.1–361.3)	265.5 (173.2–348.5)	0.22
MIP1-α	153.0 (22.7–931.8)	47.2 (17.5–91.7)	0.08
IL-8	9.5 (4.8–22.5)	32.6 (10.9–114.4)	0.003
MIP1-β	51.2 (31.9–89.9)	75.4 (43.5–131.2)	0.11
VEGF	236.2 (80.3–325.3)	214.4 (116.1–274.7)	0.93

The results are presented as median and interquartile range (25th and 75th). TNF-α: Tumor necrosis factor alpha, MCP-1: Monocyte Chemoattractant Protein-1, MIP1-α: Macrophage inflammatory protein one alpha, IL-8: Interleukin-8, MIP1-β: Macrophage inflammatory protein one beta, VEGF: Vascular endothelial growth factor. T2D: Type 2 diabetes, KPD: Ketosis-prone diabetes

Monocyte chemoattractant Protein-1

MCP-1 was significantly lower in the non-ketotic phase KPD group compared to the T2D group [median 240.4 (IQR 202.2–309.7) pg/ml vs. 276.9 (251.1–361.3) pg/ml, ($p = 0.03$)]. MCP-1 was comparable between ketotic phase KPD and T2D groups as well as between ketotic phase KPD and non-ketotic phase KPD groups (Fig. 1b).

Macrophage inflammatory protein one alpha

MIP1-α was significantly higher in T2D patients compared to ketotic phase KPD [median 30.9 (IQR 11.1–149.01) pg/ml vs. 9.5 (4.8–22.5) pg/ml, ($p = 0.03$)]. MIP1-α was significantly higher in non-ketotic KPD compared to ketotic phase KPD [median 72.8 (IQR 33.6–437.7) pg/ml vs. 30.9 (13.7–76.4) pg/ml, ($p = 0.04$)]. MIP1-α was comparable between non-ketotic phase KPD and T2D groups (Fig. 1c).

Interleukin-8

IL-8 was significantly higher in people in ketotic phase KPD than in those with T2D [median 30.9 (IQR 11.1–149.01) pg/ml vs. 9.5 (4.8–22.5) pg/ml, ($p < 0.001$)]. IL-8 was significantly higher in the non-ketotic phase KPD group compared to the T2D group [median 72.4 (IQR 10.2–140.9) pg/ml vs. 9.5 (4.8–22.5) pg/ml, ($p = 0.02$)]. IL-8 was comparable between non-ketotic phase KPD and ketotic phase KPD groups (Fig. 1d).

Macrophage inflammatory protein one beta

MIP1-β was comparable between ketotic phase KPD, non-ketotic phase KPD and T2D groups (Fig. 1e).

Vascular endothelial growth factor

VEGF was similar between ketotic phase KPD, non-ketotic phase KPD and T2D groups (Fig. 1f).

Discussion

We aimed to investigate the inflammatory profile in people with non-autoimmune diabetes. The major findings are: (i) people with KPD have elevated pro-inflammatory cytokines compared to T2D patients, (ii) ketotic phase KPD is associated with a different pro-inflammatory profile compared to the non-ketotic phase, and (iii) the inflammatory profile appears to be comparable between KPD patients in non-ketotic phase and T2D patients. However MCP-1 was lower in the non-ketotic phase KPD group as compared to the T2D group, and IL-8 was higher in the non-ketotic phase KPD group as compared to the T2D group. Based on these results, there are no clear differences in inflammatory responses between non-ketotic phase KPD and T2D patients.

Increasing evidence suggests a low grade pro-inflammatory profile is associated with insulin secretion deficiency and insulin resistance in T2D [2, 7, 26, 27]. Novel approaches suggest that pancreatic β-cell function may benefit from anti-inflammatory profile. Macrophages belongs to the major actors of inflammation through their M1 or M2 polarization. They acquire the M1 phenotype following stimulation with interferon gamma (IFN-γ) and secrete high levels of pro-inflammatory cytokines [TNF-α, IL-6, MCP-1]. M2 macrophages are stimulated by IL-4 and IL-13, and they secrete, among others, anti-inflammatory cytokines and chemokines (IL-10, TGF-β, IL-4, MIP1-α, MIP1-β, and VEGF) essential for inflammatory response resolution. Levels of pro-inflammatory cytokines secreted by M1 macrophages were found to be elevated in peripheral blood in people with T2D and have been related to impaired insulin secretion [27]. Moreover, these M1 macrophage pro-inflammatory cytokines have been identified in autopsy pancreases from T2D individuals and have been associated with insulin secretion deficiency [28].

So, as clinical relevance for this study, it is possible that higher level of some of the pro-inflammatory markers during the acute ketotic phase compared to the chronic non-ketotic phase KPD contribute for acute failure of insulin secretory response in the former phase. We have previously shown that KPD patients in the ketotic phase have poor glycemic control, higher blood glucose and lower insulin secretion compared to people with non-ketotic phase KPD and those with T2D [24]. Moreover, it has been reported previously that chronic exposure to high blood glucose has detrimental effects on insulin synthesis or secretion, cell survival, and insulin sensitivity through multiple mechanisms ("glucotoxicity"), which in turn

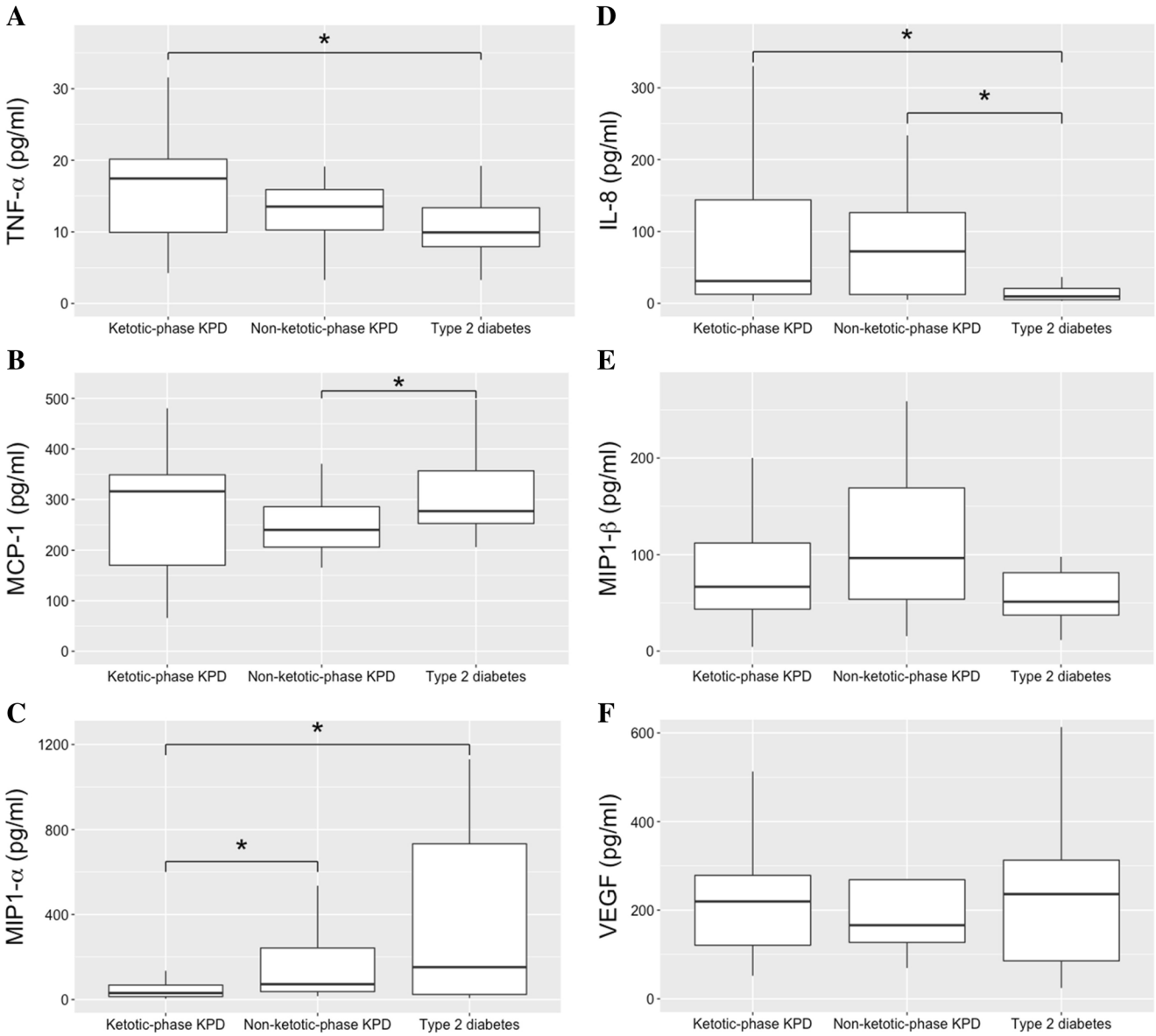

Fig. 1 Concentrations of TNF-α (**a**), MCP-1 (**b**), MIP1-α (**c**), IL-8 (**d**), MIP1-β (**e**), and VEGF (**f**) according to the diabetes phenotype (Ketotic phase KPD, non-ketotic phase KPD, and type 2 diabetes). TNF-α: Tumor necrosis factor alpha, MCP-1: Monocyte Chemoattractant Protein-1, MIP1-α: Macrophage inflammatory protein one alpha, IL-8: Interleukin-8, MIP1-β: Macrophage inflammatory protein one beta, VEGF: Vascular endothelial growth factor. KPD: Ketosis prone diabetes. The results are presented as median and interquartile range (25th and 75th). * = $p < 0.05$

lead to hyperglycaemia and to the vicious cycle of continuous deterioration of β cell function [29]. [29, 29, 29, 28, 28] However, Stentz et al., in 2004 studied inflammatory states in patients with hyperglycemic crisis at the time of presentation and after insulin therapy. The results indicated that hyperglycemia promotes inflammation, though it was unclear whether it was due to insulinopenia or hyperglycemia or both together. Return of inflammatory markers to normal levels with insulin therapy demonstrates a robust anti-inflammatory effect of insulin [30]. Viral infection may have also contributed to inflammation and to the subsequent metabolic features in KPD [21, 31]. However, a direct relationship between viruses and insulin deficiency in ketosis-prone diabetes is not clearly understood.

It is the first time that a study focus on the inflammatory profile of KPD in acute ketotic and non-ketotic phase, and from T2D during the acute hyperglycemic crisis. A limitation in our study is that we have not performed longitudinal study. Studies investigating the role of inflammation in ketosis-prone diabetes from insulin secretion deficiency at diabetes onset to recovery of β-cell function (remission) in the same cohort, followed prospectively would have provided more insight. This preliminary study is also limited by its small sample size, which prevents us from drawing any definitive conclusions.

Conclusions

This preliminary study revealed a pro-inflammatory profile in KPD compared to T2D patients. Ketotic phase KPD is associated with a different pro-inflammatory profile compared to the non-ketotic phase. The inflammatory profile appears to be comparable between KPD patients in non-ketotic phase and T2D patients. Although we evaluated peripheral blood cytokine levels, our results may reflect what is happening in β-cells during the ketotic phase in KPD. β-cells may be exposed to a highly pro-inflammatory environment, and an individual's ability to counterbalance this phenomenon may predict their level of insulin deficiency leading to production of ketone bodies. Further studies following patients' inflammatory profiles from ketotic phase to remission are therefore needed. Whether this inflammatory profile will directly impact the natural history of β-cell function and distinguish insulin-dependent KPD from KPD during their remission period needs further investigation.

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Authors' contributions ELY, ES, JFG and JCM: study design and conception, data collection and analysis, and drafting of the manuscript. PB, JLN: data analysis and drafting of the manuscript. JJN, VK, END, BAT, MAK, MT, GL, MYD: data interpretation, editing and review of the manuscript. All authors read and approved of the final manuscript.

ELY, ES, JFG and JCM are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Compliance with ethical standards

Ethics approval and consent to participate This study was performed in accordance with the guidelines of the Helsinki Declaration and was approved by the National Ethics Committee of Cameroon. All participants provided written informed consent.

Consent for publication Not applicable.

Competing interests The authors declare that they have no competing interests.

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