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Fibroblast growth factor 23 in acute burn patients: Novel insights from an intact-form assay

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ABSTRACT

Introduction: Fibroblast growth factor 23 (FGF23) is a key regulator in phosphate and vitamin D metabolism When measured with c-terminal assay, it has been shown to be increased following burn. Progress in understanding FGF23 physiology has emphasized the importance of assessing the intact form of FGF23.

Methods: The present cohort study is a complementary analysis of a previously published work. Patients >18 years, admitted within 24 h after injury with burn surface area (BSA) >10% were included. C-terminal (c-term) and intact (i) FGF23 assay were performed at admission and every week during 4 weeks of follow-up. Inflammation and iron status were assessed at the same time points.

Results: Twenty patients were initially included and 12 were followed until day 28. The c-term FGF23 tended to gradually increase during the 4 weeks of follow-up while iFGF23 was quite stable into normal ranges. Iron status showed a typical inflammatory profile. C-term FGF23 was significantly positively correlated with c-reactive protein (CRP) and negatively correlated with iron levels. iFGF23 was not correlated with CRP or iron.

Conclusion: FGF23 status following burn is characterized by a dissociation between c-term FGF23 and iFGF23. The hypothesis of an increased cleavage may be raised. Respective role of inflammation and iron levels in such deregulation need to be specified. Both c-term and intact assays should be performed in further studies aiming to increase knowledge on FGF23 regulation and effects in burn patients.

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1. Introduction

Fibroblast growth factor 23 (FGF23) is a bone derived hormone that is implicated in phosphate (P) and vitamin D (VD) regulation. It is produced mainly by osteocytes, but also by osteoblasts, osteoprogenitor cells, cementoblasts, odontoblasts, and chondrocytes [1]. FGF23 binds the FGF receptor – αKlotho complex. FGF receptor (FGFR) is broadly expressed, while the co-receptor αKlotho is expressed only in a few

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tissues including kidney, parathyroid or pituitary. The primary target of FGF23 is the kidney where it regulates genes of 2a sodium/phosphate cotransporter and 1α-hydroxylase, leading to phosphate excretion and inhibition of 25 hydroxyvitamin D (25(OH)-D) hydroxylation [2]. In addition, FGF23 is able to stimulate expression of the vitamin D 24-hydroxylase, thus increasing 25(OH)-D and 1,25 dihydroxyvitamin D ($1,25(OH)_2$-D) inactivation. The principal regulators of FGF23 are thought to be P and $1,25(OH)_2$-D levels. However, the regulation of FGF23 expression is complex and still incompletely understood.

Burn induces significant physiologic changes involving cardiovascular system, immune system, metabolism or electrolyte balance. In particular, severe hypophosphatemia is frequently observed in acute burn patients. The exact mechanism of this phenomenon is not fully known but probably involves various factors such as type and quantity of fluid resuscitation, acid-base disturbances, electrolytes imbalances catecholamines or exudative losses [3,4]. Hypophosphatemia may have significant consequences in term of cellular membrane integrity or energy metabolism. From another point of view, burn has repercussions on VD synthesis due to skin damage and, later, strategies to prevent abnormal scarring following burn healing (sunlight eviction and pressure garments). Furthermore, alterations of VD physiology and metabolism may be suspected in severe burn patients who are thus at high risk of VD deficiency [5]. Given its role in P and VD metabolism, it may be therefore relevant to focus on FGF23 in the particular context of burn.

In a previous work [6], we studied blood levels of c-terminal FGF23 (c-term FGF23) in adult burn patients during acute care. However, FGF23 status may be even more complex than reported, due to the processing of the FGF23 protein (Fig. 1). FGF23 is initially expressed as a 251-amino acid protein. The signal peptide (the 24 first amino acids) is then cleaved off to produce the mature protein, which is considered biologically active. This last molecule is secreted intact or cleaved within bone cells. The proteolytic cleavage site is located between amino acid 179 and 180 (the RXXR region) and is thought to be recognized by subtilisin-like protein convertases such as furin. Cleavage results in production of the two inactive N-terminal and C-terminal fragments. Glycosylation of FGF23 by polypeptide N-acetylgalactosaminyltransferase 3 (GALNT3) seems to prevent cleavage [2].

There are currently two strategies to quantify circulating FGF23 concentrations, detecting different hormone's forms. The c-term enzyme-linked immunosorbent assay (ELISA) recognizes both intact hormone and C-terminal fragment, while the intact ELISA only recognizes the full-length mature hormone (Fig. 1).

In the past few years, knowledge about FGF23 physiology, processing and regulation has improved. Particularly, impact of iron deficiency on FGF23 production and cleavage has been cited in different clinical conditions [2,7]. Moreover, new commercial intact assays were recently available at more affordable terms. Using frozen blood samples from adult burn patients included in our previous study [6], the objective of the present analyses was to explore intact FGF23 in conjunction with iron and inflammation status. Indeed, data about intact FGF23 have not yet been reported in the specific context of burn.

2. Methods

This cohort study was conducted from March 2012 to January 2013 in a 6-bed burn unit after approval by the local Ethics Committee of our University Hospital (Ref B707201213417, 6th March 2012). Informed consent was obtained from the patients or their relatives prior to enrolment.

The details of the study design have been previously published [6]. In summary, Caucasian patients over 18 years, with a burn surface area (BSA) greater than 10% and admitted within the first 24 h following injury were included. Pregnancy, renal or liver failure, prior vitamin D substitution were considered exclusion criteria. They benefited from local standard monitoring and care procedures in term of fluid resuscitation, nutrition and surgery. They daily received vitamin D3 (cholecalciferol, VD3) from nutrition and multivitamin complex supplementation, reaching a daily dose of 600 to 800 UI. Patients did not receive any iron supplementation. Iron intakes ranged around 20 mg per day, provided by hospital made menu, enteral nutrition (Fresubin® HP Energy, Fresenius-Kabi, Germany), oral nutritional supplements

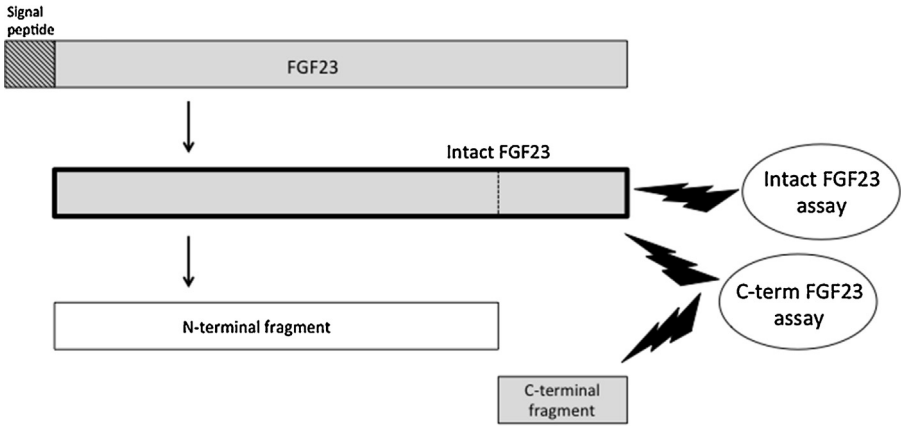

Fig. 1 – Processing of FGF23 protein.

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(Fresubin® 2 kcal, Fresenius-Kabi, Germany or Resource® 2.0 fibres, Nestle, Switzerland) or micronutrient complex (Supradyn® Energy, Bayer, Germany). A restrictive and individualized strategy was applied for red blood cell (RBC) transfusion.

Blood samples were collected at admission (D0) and then every week during the first month of in-hospital follow-up. Blood was notably drawn in serum gel tube (Venosafe Plastic Tubes, Terumo, Haasrode, Belgium) before being centrifugated (3500 rpm, 15 min, 4 °C). Supernatant was finally frozen and stored at −80 °C. Similarly, blood was also drawn in lithium heparin gel tube.

C-term and intact FGF23 concentrations were determined with ELISA method (Immunotopics®, Immunotopics International, San Clemente, CA, USA). Normal ranges were respectively 30–176 RU/ml and 8.6–72.8 pg/ml. In our lab, the coefficient of variation of both assays was <10%. Creatinine, phosphate and C-reactive protein (CRP) blood concentrations were determined with Cobas® automate (Roche, Mannheim, Germany). 1,25$(OH)_2$-D was assayed with iSYS® automate (IDS, Boldon, UK). Iron status was assessed using the same automate. Iron, ferritin and transferrin were measured using spectrophotometric assay, chemiluminescence immunoassay and immunoturbidimetric assay, respectively. Serum transferrin saturation (TSAT) was calculated using the following formula: TSAT = iron (μmol/l)/[transferrin (g/l) × 25].

Urine samples were collected at the same time as blood samples. Urine levels of phosphate was assayed with Cobas® automate (Roche, Mannheim, Germany). The fractional excretion (FE) of phosphate was calculated according to the following equation: FE P = (urine P × plasma creatinine)/(plasma P × urine creatinine) × 100.

Statistical analysis was performed using Graphpad Prism (version 6.0 for Mac OSX, Graphpad Inc., San Diego, CA, USA). Data were tested for normality using the Shapiro–Wilk test. Results are expressed as medians and ranges (min–max). Paired data (at D0 and D28 for the 12 patients who completed the study) were compared using Wilcoxon test. Unpaired data were compared using Mann–Whitney test. Proportions were compared using Fisher's exact test. Correlations were assessed using nonparametric Spearman test. A p value <0.05 was considered to be statistically significant.

3. Results

In the previous study, 24 patients were included. Frozen blood was available in 20 patients for the present secondary analysis. There were 2 women and 18 men. Median age was 44 (19–86) years old, median BSA reached 15 (7–85) % and median ABSI (Abbreviated Burns Severity Index) score was 5 [4–12]. Of the enrolled patients, 8 were discharged before the end of the protocol. The 12 remaining patients received 7 (2–25) RBC units during the month of follow-up.

Evolution of c-term FGF23 and iFGF23 at each time point for the 12 patients who completed the study is shown in Fig. 2. The c-term FGF23 tended to gradually increase during the 4 weeks of follow-up. However, there was no statistical difference between concentrations at inclusion and at the end of the protocol when comparing the 12 patients who completed the study. iFGF23 was quite more stable into normal ranges. Iron status is detailed in Table 1. Iron significantly decreased between D0 and D28 ($p = 0.0078$). Ferritin tended to increase at D28, without reaching significance. Transferrin tended to be higher at admission than later during hospitalization, again without reaching significance. Interestingly, the proportions of normal c-term FGF23 at D0 and D28 were similar to those of normal iron (Table 2). In the same way, iron concentrations were negatively correlated to c-term FGF23: the nonparametric Spearman correlation coefficient (r) was −0.44 (95% CI: −0.71 to −0.05, $p = 0.0233$). No correlation was found between c-term FGF23 and ferritin. Contrary to the previously described correlation between c-term FGF23 and CRP ($r = 0.59$, 95% CI:0.22–0.82, $p = 0.0032$), iFGF23 was not correlated to CRP. While there was no correlation between iFGF23 and iron, a negative correlation was found between iFGF23 and ferritin: r was −0.45 (95% CI: −0.71 to −0.07, $p = 0.0179$).

At D28, no significant difference was observed between patients with BSA <20% or patients with BSA ≥20% regarding c-term FGF23 and iFGF23. Three of the 12 patients who completed the study had BSA ≥40%. When compared to the nine other patients with lesser injury, c-term or iFGF23 levels were not statistically different.

Creatinine level was into normal ranges at inclusion and gradually decreased during the next 4 weeks to reach 6.3 (4.9–11) mg/l. Phosphate levels remained into normal ranges during all the protocol (Table 1). Fractional excretion of phosphate significantly decreased after 28 days. There was no significant change in 1,25$(OH)_2$-D concentration over the study period.

4. Discussion

FGF23 is a key regulator of phosphate and vitamin D. It is the subject of a growing research but little is known about its evolution in the context of burn. We previously highlighted a positive correlation between c-term FGF23 and CRP. We presently aimed to complete these data by looking at the intact portion of the FGF23 protein. Interestingly, c-term FGF23 and iFGF23 did not show a similar evolution following burn. While c-term FGF23 tended to increase over time and was positively correlated with CRP, iFGF23 mostly stayed into normal ranges, without any correlation with the inflammation marker.

Hypophosphatemia is commonly observed in burn patients during acute phase [3]. FGF23 is a potent phosphaturic factor [6]. Based on our previous results showing a progressive increase in cFGF23 levels after burn, the potential role of FGF23 in burn related hypophosphatemia has been raised. Nonetheless, in the present analysis, iFGF23 was not found increased. This finding now questions our previous assumption. FGF23 cannot be involved in hypophosphatemia if the intact form, which is the active form, is not increased. This normal intact form is in line with the results of FE P and 1,25$(OH)_2$-D, that could not be explained with the only c-term FGF23 values.

In the present study, phosphatemia remained into normal range due to the regular clinical practice of phosphate supplementation in case of low phosphate levels. Theoretically in healthy people, phosphate intakes should lead to an increase in both c-term and iFGF23, and the increase was greater for iFGF23 than for the c-term FGF23 [8]. In acute burn

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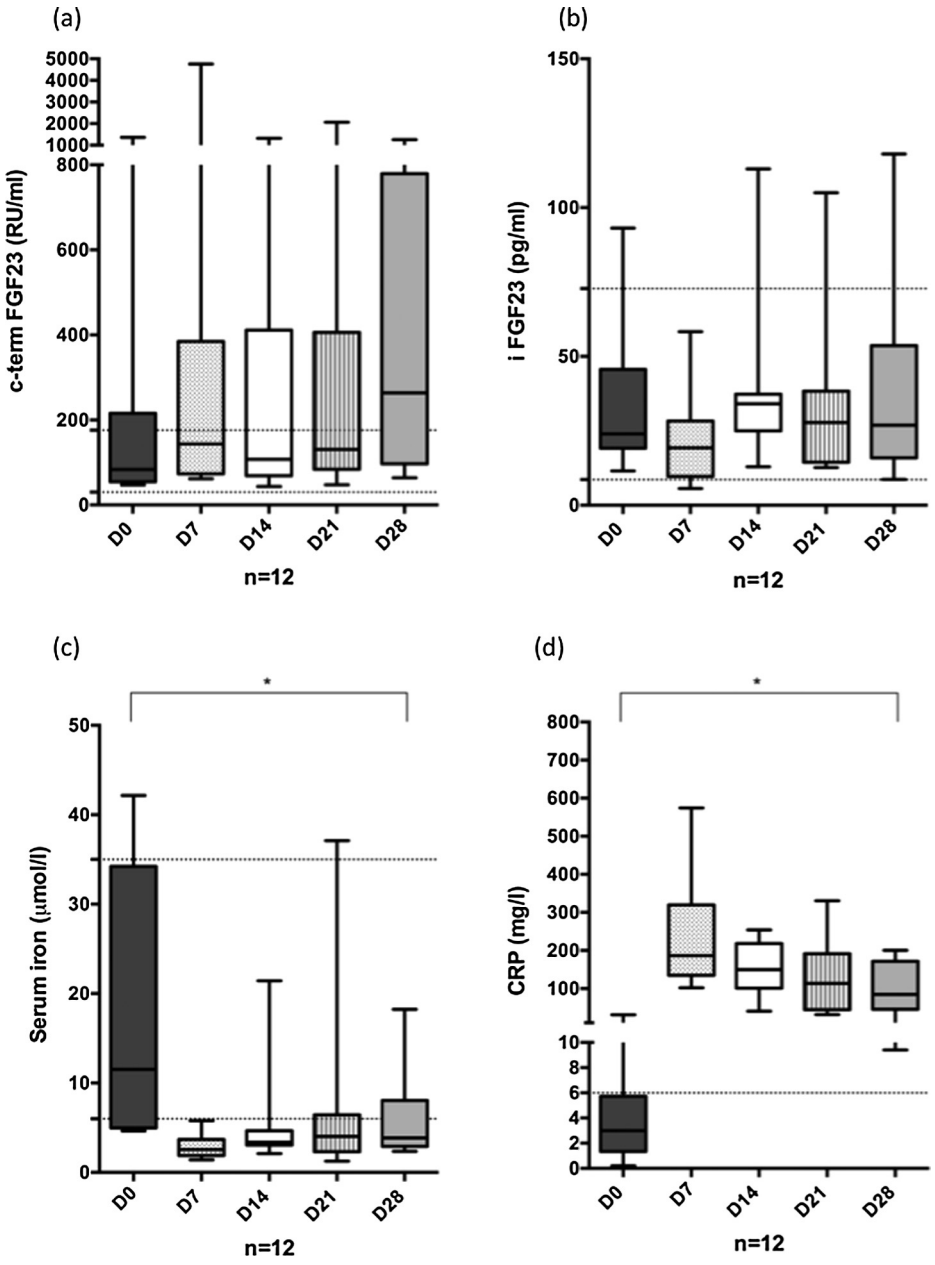

Fig. 2 – Median and ranges (min–max) of c-term FGF23 (a), iFGF23 (b), iron (c) and CRP (d) at admission (D0), day 7 (D7), day 14 (D14), day 21 (D21) and day 28 (D28), for the 12 patients who completed the study. Dotted lines represent normal ranges. *$p < 0.05$.

patients, such profile was not observed at all. This could be explained by an increased cleavage of the intact form in the context of burn. Indeed, literature has recently brought insights on FGF23 regulation. Gene expression is not the only process to be regulated: proteolytic cleavage of the mature FGF23 has now to be considered as the second level of FGF23 regulation [2,7]. Cleavage may be influenced by several factors or pathological conditions. Among them, some pro-inflammatory mediators have recently been confirmed as FGF23 production and cleavage regulators [9]. Iron level is another described regulator. A trial in women with iron deficiency confirmed its role in FGF23 regulation, showing elevated levels of c-term FGF23 but normal iFGF23 concentrations [10]. Burn represent a complex condition, resulting in inflammation that may be systemically extended and that may in turn impact iron status. Actually, iron levels are known to be low in burn patients [11], As anticipated, the present data confirmed the inflammatory status and the low iron levels following burn, without any influence of RBC transfusions. The increased cleavage that is suspected in the present burn patients could be due to inflammation and/or low iron levels. Their respective roles need to be defined. Likewise, the mechanism of such regulation is still poorly understood. Very recent animal data suggest that inflammation stimulates a specific nuclear transcription factor, the hypoxia-inducible factor 1α (HIF1α). Secondary to inflammation, functional iron deficiency could in

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Table 1 – Lab data at admission (D0), day 7 (D7), day 14 (D14), day 21 (D21) and day 28 (D28). Data are expressed as median and ranges (min–max). Paired data (at D0 and D28 for the 12 patients who completed the study) were compared using Wilcoxon test ($p < 0.05$ is considered significant). FE P, fractional excretion of phosphate; TSAT, serum transferrin saturation; CRP, C-reactive protein; NR, normal ranges.

Serum markers	NR	D0 ($n = 20$)	D7 ($n = 18$)	D14 ($n = 16$)	D21 ($n = 13$)	D28 ($n = 12$)	p value
c-term FGF23	30–176 RU/ml	62.45 (35.7–1363)	85.65 (36.5–4753)	94.3 (28–1321)	89.8 (28.9–2067)	263.7 (63.6–1259)	0.1099
iFGF23	8.6–72.8 pg/ml	24.9 (11.5–93.1)	29.5 (5.6–142)	36 (12.9–154)	32 (12.7–135)	32.45 (8.6–118)	0.3223
Phosphate	0.74–1.51 mmol/l	1.13 (0.49–1.63)	1.06 (0.38–1.37)	1.08 (0.77–1.59)	1.13 (0.55–1.38)	1.05 (0.48–1.64)	0.9097
FE P	<20%	12.24 (2.1–31.87)	5.57 (0.99–18.19)	9.05 (0.47–16.6)	14.84 (6.04–32.1)	6.46 (0.47–16.53)	**0.0098**
$1,25(OH)_2$-D	<85 pg/ml	50 (22–78)	42.5 (19–105)	41 (19–69)	31.5 (19–102)	34.5 (19–63)	0.1250
Iron	6–35 μmol/l	13 (4.5–42.1)	3 (1.1–7.7)	4.2 (2.1–22.31)	4.1 (1.2–37.1)	3.9 (2.4–18.2)	**0.0078**
Ferritin							
Male ($n = 18$)	34–100 μg/l	222.7 (84.6–1683)	564.1 (314.3–1683)	588.9 (155.5–1647)	406.5 (140.7–2886)	632.5 (198.6–1017)	0.7344
Female	15–150 μg/l	1095 (354–1835)	1255 (559.1–1950)	1633 (873.9–2392)	1320 (553.6–2087)	3583 (2576–4589)	-
Transferrin	1.6–3.5 g/l	1.9 (1.1–2.5)	1.3 (0.3–1.8)	1.3 (0.5–2.1)	1.3 (0.5–2)	1.3 (0.7–2.1)	0.8438
TSAT	0.2–0.5	0.3 (0.2–0.8)	0.1 (0–0.5)	0.1 (0.1–0.5)	0.2 (0–0.9)	0.1 (0.1–0.4)	**0.0078**
CRP	0–6 mg/l	3 (0.2–31.3)	147 (16.1–574.4)	102.6 (5.8–254)	80 (14.8–330)	84.6 (9.4–200.4)	**0.0005**

turn stabilize HIF1α, increasing FGF23 expression. In parallel, both inflammation and low iron levels may possibly act on FGF23 glycosylation or on proteolytic enzymes, leading to an increased FGF23 cleavage [12].

No differences were observed about c-term FGF23 or iFGF23 levels between minor burn patients and more severe burn patients. One could suspect that larger BSA would result in higher c-term FGF23 levels. This hypothesis should at best be tested in a further study including a greater number of patients.

Some limitations need to be considered in the present trial. First, FGF23 stability after prolonged storage at −80° was not tested. The potential impact of FGF23 biodegradation on intact FGF23 levels is unknown. However, storage was under continuous temperature monitoring and blood samples were not submitted to repeated thawing. Second, the kidney function was assessed using blood creatinine levels. It is now well known that FGF23 increases in case of renal failure. In CKD patients, both iFGF23 and c-term FGF23 increase with the progressive loss of renal function [7]. FGF23 changes in acute kidney injury (AKI) are less obvious, as iFGF23 was not often measured in the published reports [13]. In such context, secretion of FGF23 is thought to be increased, associated to a reduced renal clearance, thus increasing the blood c-term FGF23 [14]. The only relevant data regarding intact portion come from a murine model of AKI, in which both c-term FGF23 and iFGF23 increased at 24 hours after injury induction [15]. Blood creatinine level is not a sensitive and specific marker of kidney function, especially in critical care patients experiencing fluid shifts and muscle catabolism. Cystatin C is probably a more valid marker in a critical care context [16,17] but it is not widely available in daily practice. However, using creatinine levels instead of more accurate strategies does not seem to have influenced results as FGF23 profile in case of kidney failure differs from the profile reported in the present study.

Despite the low number of included patients, this study is the first to focus on intact FGF23 in burn patients. The FGF23 regulation is complex and context dependant. It affects not only gene expression but also the mature protein cleavage. From our data, we can postulate that burn is associated with a disrupt balance between production and cleavage, resulting in dissociation between c-term FGF23 and iFGF23. The respective role of inflammation and low iron levels in FGF23 regulation need to be further explored. In the next future, both c-term FGF23 and iFGF23 assays will have to be performed when dealing with patients experiencing inflammatory diseases such as our model of burn. Ideally, the ratio intact assay/c-term assay could be a relevant marker of FGF23 bioactivity. However, to date, values obtained by the two different kits are difficult to convert. Finally, our results rule out FGF23 as one of the causes of burn-related hypophosphatemia, as previously hypothesized.

Table 2 – Numbers and percentages of patients into normal ranges at D0 and D28.

Lab test	D0	D28	p value
c-term FGF23	9/12 (75%)	5/12 (42%)	0.2138
iFGF23	11/12 (92%)	9/12 (75%)	0.5901
Iron	9/12 (75%)	5/12 (42%)	0.2138

Conflict of interest

Each author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author's contribution

AFR, JCS, EC designed and conducted research, AFR, JCS and EC analyzed data, AFR and EC wrote paper, JCS, PDe and PDa critically reviewed paper. All authors approved the final manuscript.

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