Anterior and Posterior Pituitary Function in Patients with Sheehan Syndrome – Combining the use of Insulin Tolerance Test and Copeptin Assay

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Abstract

Introduction: Sheehan syndrome (SS) typically involves the loss of anterior pituitary cells and rarely affects the posterior pituitary. The water deprivation test (WDT) is the gold standard for diagnosing central diabetes insipidus (CDI), but it is cumbersome. Serum copeptin measurements are an alternative for CDI diagnosis. In this study, we measured hypoglycaemia-stimulated serum copeptin in SS patients to assess posterior pituitary function alongside anterior pituitary hormone levels. **Methods:** This study recruited 43 patients with SS on stable hormonal replacement except for growth hormone (GH), 18 patients with CDI, and 19 body mass index (BMI) and parity-matched controls. All patients with SS and four patients with CDI underwent an insulin tolerance test (ITT), and hypoglycaemia-stimulated copeptin levels were measured at 0, 30, 45, and 90 minutes after insulin injection. **Results:** The mean serum copeptin level among patients with SS (26.01 ± 12.41 pmol/L) was significantly lower than that in healthy controls (31.92 ± 7.85 pmol/L) and higher than that in patients with CDI (1.81 ± 0.14 pmol/L). Using pre-defined cut-offs for CDI, basal serum copeptin <2.69 pmol/L and stimulated levels <4.92 pmol/L for complete central DI, and basal copeptin levels >2.69 pmol/L and stimulated copeptin <4.92 pmol/L for partial central DI, 9.2% (n = 4) of patients with SS had CDI, of which half had complete CDI and half had partial CDI. **Conclusion:** A significant number of patients with SS who are on hormone replacement therapy show involvement of the posterior pituitary, despite not displaying symptoms.

Keywords: Copeptin, diabetes insipidus, posterior pituitary, sheehan syndrome

INTRODUCTION

Sheehan syndrome (SS) is a common cause of hypopituitarism in developing nations.[1-3] The pituitary gland (PG) enlarges during pregnancy because of the effect of placental hormones mainly oestrogen.[4] Any insult like hypotension because of post-partum haemorrhage (PPH) results in ischaemic necrosis of the anterior pituitary. In addition to PPH, many other factors also play some role in pituitary necrosis. These include small sellar volume, autoimmunity, and coagulation abnormalities.[2,4,5] Ischaemic necrosis of PG mostly involves the anterior pituitary, resulting in the deficiency of almost all the anterior pituitary cell lines.[6] Somatotroph and thyrotroph cells are involved in all cases of SS, and preservation or recovery of gonadotroph, lactotroph, or corticotroph cells is reported in a few such patients.[7-9] Because of the advantageous blood supply, posterior pituitary involvement is less common,[2,10] even though histological examination many years after the initial insult reveals some scarring and atrophy of the posterior pituitary as well.[11] Central diabetes insipidus (CDI), either partial or complete, is reported in 5% of patients with SS when assessed by water deprivation test (WDT).[1]

Arginine vasopressin (AVP) is released from the posterior pituitary in response to an increase in serum osmolality. Sub-optimal release of AVP in response to water deprivation or saline loading (both increasing serum osmolality) is diagnostic of CDI.[12] Three previous studies have reported

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subtle posterior pituitary dysfunction in a small number of patients with SS by using WDT or saline loading with variable results.[13-15] One study also measured AVP levels post 5% saline loading to assess posterior pituitary dysfunction in them.[16] Insulin-induced hypoglycaemia simultaneously tests the anterior pituitary (GH, PRL, and cortisol) as well as the posterior pituitary (release of AVP) function.[17,18] Copeptin, the C-terminal part of the AVP precursor, remains stable for many days even at room temperature[19] and is increasingly being used for the diagnosis of CDI. In a single study, after pituitary surgery, the measurement of copeptin during insulin-induced hypoglycaemia correctly diagnosed patients with CDI.[18] Copeptin response to hypoglycaemia has not been studied in patients with SS, some of whom may have CDI. The aim of the present study was to simultaneously test anterior and posterior pituitary hormone response to insulin-induced hypoglycaemia in stable patients of SS on regular follow-up.

METHODS

Study participants

This case-control study was carried out at the Endocrinology department of a tertiary care hospital in North India. The study included patients diagnosed with SS who were on regular follow-up in the department. SS was defined as the presence of the following criteria: (a) typical obstetrical history of severe PPH; (b) severe hypotension or shock, for which blood transfusion or fluid replacement was necessary; (c) failure of postpartum lactation; (d) failure to resume regular menses after delivery; (e) varying degree of anterior pituitary insufficiency; (f) partial or complete hypopituitarism; and (g) a partially or completely empty Sella on a computed tomography (CT) scan or magnetic resonance imaging (MRI).[1,3] For comparison, 18 patients diagnosed with CDI and 19 healthy women [controlled for body mass index (BMI) and parity] were also included. CDI patients were diagnosed based on a water deprivation test (WDT). Nineteen seemingly healthy women were selected as controls from the community and were counselled about the study protocol. Subjects with persistent hypokalaemia, hypercalcaemia, psychiatric illness, uncontrolled diabetes mellitus, taking medications known to cause polyuria, and those with other causes of hypopituitarism were excluded from the study.

All the study participants received a detailed clinical assessment. Relevant history focusing on menstrual disturbances (amenorrhea, oligomenorrhoea), lactational failure following the last child birth, and symptoms of hypothyroidism and hypocortisolism was noted. In addition, a history of drug intake, urine volume, headache, and visual disturbances was also noted. Subjects were examined for blood pressure (BP) and anthropometry such as height, weight, waist circumference (WC), and hip circumference (HC). Measurements were performed with patients barefoot in light clothing and by a single examiner. Height was measured with a wall-mounted Stadiometer (SECA 13, Hamburg, Germany). Body weight (in kg) was measured on a digital

scale balance (SECA 13, Hamburg, Germany). WC was measured midway between the lowest rib margin, and iliac crest while HC was measured at the widest levels over the greater trochanters.

Insulin tolerance test

Patients were admitted for 1 day, and the test procedure was carried out as follows: blood sampling was done after an overnight fast. The basal sample was taken after inserting an intravenous (IV) cannula 30 minutes prior to collection. Blood was drawn for basal measurement of glucose, GH, cortisol, PRL, and copeptin. Following this, insulin (0.1–0.2 U/kg) was injected IV and additional blood samples were drawn at 30, 45, and 90 minutes for repeat measurements of blood glucose, GH, cortisol, PRL, and copeptin. One patient experienced hypoglycaemic seizures, which were promptly resolved with intravenous dextrose. No other significant adverse effects occurred during ITT.

Assays

A baseline early-morning fasting blood sample was drawn in all patients with SS, CDI, and controls for the following investigations: haemoglobin (Hb), total leucocyte count (TLC), platelet count, urea, creatinine, bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein, albumin, glucose, glycated haemoglobin (HbA1c), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), calcium (Ca), phosphorous (PO_4), uric acid (UA), triiodothyronine (T3), tetra Iodothyronine (T4), thyroid stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinising hormone (LH), insulin-like growth factor-1 (IGF-1), growth hormone (GH), prolactin (PRL), cortisol, and copeptin. The blood was allowed to clot at room temperature (15°C–25°C) and centrifuged for 15 minutes to obtain haemolysis-free serum. The serum was collected in separate plastic tubes, and some parts were stored at −70°C till further analysis. All patients with SS and four with CDI underwent ITT. In healthy controls and 14 CDI patients, only basal samples after an overnight fast were taken. Serum and urine osmolality was measured after an overnight fluid restriction by the principle of freezing-point depression method on an osmometer (Advanced Instruments, INC. Massachusetts 02062, USA).

Measurement of glucose, urea, creatinine, bilirubin, ALT, ALP, total protein, and albumin was carried out on the same day on an automated chemistry analyser (HITACHI-912). Plasma glucose was estimated by enzymatic method using glucose oxidase and peroxidase on the same automated chemistry analyser. HbA1c was measured using ion-exchange high-performance liquid chromatography on a TOSOH HbA1c analyser (HLC 723G8, TOSOH India Pvt Ltd). with whole blood collected in ethylene diamine tetra acetic acid (EDTA) tube. Serum PRL [normal range: 1–27 μg/L (women)], TSH, T3, T4, FSH, LH, cortisol, and GH were measured by chemiluminescence assay on Unicel DXI 800 (Beckman Coulter) by using US

FDA-approved reagents. IGF ELISA kit was used to measure serum IGF-1 (DEMEDITEC Germany, DE4140) (detection range: 4.081–600 ng/mL, coefficient of variation {CV} for intra-assay as <7.4%, and inter-assay as <14.8%). Serum copeptin was measured using a commercially available ELISA kit (CEA365Hu) (detection range: 1.32–248.7 pmol/L, CV for intra-assay as <10%, and inter-assay as <12%).

Imaging

All subjects with SS and CDI underwent MRI of the sella and suprasellar region with dynamic contrast study by using a Siemens 1.5 tesla machine. Pre-contrast T1- and T2-weighted spin-echo coronal and sagittal sections were acquired using a small field of vision (20 × 25 cm), thin slices (3 mm), and a high-resolution matrix (256 × 512).

Definitions

Lactotroph deficiency was defined as failure of post-partum lactation and or basal serum PRL of <2 ng/mL or peak rise of <200% from baseline post-ITT. Somatotroph deficiency was defined as basal serum IGF-1 level below the reference range for age/sex and peak serum GH levels of <3 ng/ml after ITT. Gonadotroph deficiency was defined as secondary amenorrhea and serum LH or FSH <10 IU/mL. Thyrotroph deficiency was defined as serum total T4 <4 ug/dL with TSH low or inappropriately normal, and corticotroph deficiency was defined as serum basal 8 am cortisol <3 ug/dL or peak serum cortisol <18 ug/dL after ITT.

Complete SS: Presence of more than two pituitary hormone deficiencies. Partial SS: presence of at least one pituitary hormone deficiency.[7]

Based on the copeptin assay, complete CDI was defined as basal serum copeptin of <2.69 pmol/L and peak serum copeptin of <4.92 pmol/L after insulin-induced hypoglycaemia, and partial CDI was defined as basal serum copeptin >2.69 pmol/L and peak serum copeptin of <4.92 pmol/L after ITT.[20,21]

Statistical analysis

All statistical analyses were performed using SPSS software, version 22 (SPSS Inc., Chicago, IL, USA). The normality of all the variables was tested using Kolmogorov–Smirnov test. Baseline variables among different groups were presented as mean and standard deviation (SD). Variables were summarised with repeated measures ANOVA for comparisons within and between group effects on the key outcomes. The model includes an intervention group (2 groups) x time (4 time points) as fixed factors for the outcome measures (serum copeptin, serum cortisol, serum PRL, serum GH). If there were significant interactions, the post-hoc analysis was done using Tukey's HSD (equal variances) or Games-Howell (unequal variances). The homogeneity of variance (sphericity) was checked by Mauchly's test of sphericity. The Greenhouse-Geisser correction was done in case the sphericity assumption was violated. All the tests were conducted two-sided, and a *P* value of < 0.05 was considered statistically significant.

Ethical aspects

Informed consent was obtained from all the enrolled participants. The study period extended from April 2021 to October 2022. The study was carried out in accordance with the Helsinki Declaration for medical research involving human subjects and was approved by the institutional ethics committee under protocol number #RP 203/2021.

RESULTS

Baseline characteristics of patients with SS, CDI, and controls

Forty-three patients with SS, 18 with complete CDI, and 19 healthy controls were included in the study. The features of patients with SS were as follows: mean parity was 3.02 ± 1.61, with 58.1% home deliveries. History of PPH, lactation failure, and secondary amenorrhea was present in 95.3%, 97.7%, and 93% of patients, respectively. In total, 88.37% (n = 38) patients had complete SS and 11.63% (n = 5) had partial SS. Only 39.5% (n = 17) of patients received blood transfusions. The mean duration of disease was 20 ± 6.62 years (range: 6–32 years), while the mean duration of treatment was 15.51 ± 5.8 years (range: 5–28 years). Corticotroph, gonadotroph, thyrotroph, somatotroph, and lactotroph deficiency were present in 95.3%, 93%, 100%, 97.7%, and 95.3% of patients, respectively. On MRI, 76.7% (n = 33) had complete empty sella, while 23.3% (n = 10) had partial empty sella. Patients were on replacement with a mean prednisolone dose of 3.08 ± 1.31 mg and a mean levothyroxine dose of 87.79 ± 19.95 mcg per day [Table 1].

Patients with CDI consisted of five with craniopharyngioma, and one each with lymphocytic hypophysitis, macroadenoma with apoplexy, and diabetes insipidus diabetes mellitus optic atrophy deafness syndrome (DIDMOAD). The rest of the patients had idiopathic CDI.

Hormones and markers of water metabolism in three groups

The clinical features, osmolality parameters (e.g., serum sodium, plasma, and urine osmolality), anterior pituitary hormones, and basal copeptin are given in Table 2. Urine volume, plasma osmolality, and plasma sodium were higher in patients with SS compared with controls, though it did not achieve statistical significance. Similarly, basal copeptin was significantly less in patients with SS compared with healthy controls (*P* < 0.05).

Pituitary hormones and copeptin response to hypoglycaemia in women with SS and CDI

Insulin tolerance test was performed in all patients of SS and four patients with CDI. Blood glucose decreased to <40 mg/dL at 30 minutes and to <38 ± 7 mg/dL at 45 minutes after insulin injection. Catching up with falling blood glucose, copeptin correspondingly increased with the peak at 45 minutes after insulin injection [Figure 1]. Among women with SS, four out of 43 had CDI (two had complete and two had partial).

Table 3 gives the details of basal and stimulated copeptin in patients of SS with and without CDI and four patients with diagnosed CDI. Mean basal copeptin was 2.81 ± 0.31 pmol/L in women of SS with CDI against 28.39 ± 10.38 pmol/L in those without CDI. The maximum stimulated copeptin in SS with CDI at 45 minutes of ITT was 4.08 ± 0.84 pmol/L. Age, parity, and duration of disease were greater in women with SS and CDI compared with those without DI [Table 4]. Patients of SS with complete CDI were symptomatic and required oral desmopressin supplementation, while those with partial CDI were asymptomatic.

DISCUSSION

While evaluating the anterior pituitary function using ITT in a cohort of women with SS, we simultaneously studied the posterior pituitary function by the measurement of basal copeptin and its response to insulin-induced hypoglycaemia. In addition, basal copeptin was measured in matched controls and patients with confirmed CDI. We documented the presence of posterior pituitary dysfunction in around 9% of patients with SS, which was asymptomatic in most of the patients.

In previous extensive studies on SS, the symptoms of CDI are rarely mentioned as one of its presentations.[3,22] While studies on SS have indeed documented abnormalities in AVP secretion, only a few have diagnosed CDI in a substantial number of patients with SS.[13-16] For instance, in one study, 20 patients with SS and 12 healthy controls underwent WDT and saline loading. The plasma osmolality was observed to be higher and urine osmolality lower in women with SS compared with healthy controls,[13] but none of the subjects qualified as having CDI. Similarly, in another study involving 15 women with SS and six age-matched healthy controls, no
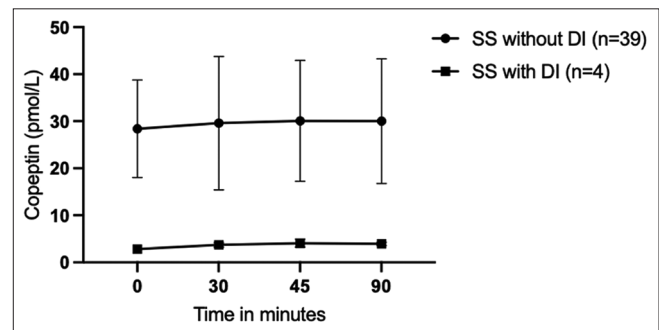
Table 1: Baseline characteristics of SS patients (*n*=43)

Parameters	Mean/*n*	SD/Percentage
Age at onset (years)	34.2	4.1
Parity	3.02	1.61
Home delivery	25	58.1%
Mode of delivery (vaginal/LSCS)	34/9	79.1%/20.9%
Postpartum haemorrhage	41	95.3%
Lactation failure	42	97.7%
Secondary amenorrhea	40	93.0%
Complete SS	38	88.37%
Partial SS	5	11.63%
Duration of disease (years)	20.41	6.62
Duration of treatment (years)	15.51	5.8
Corticotroph deficiency	41	95.3%
Gonadotroph deficiency	40	93.0%
Thyrotroph deficiency	43	100%
Lactotroph deficiency	41	95.3%
Somatotroph deficiency	42	97.7%
MRI (complete/partial ES)	33/10	76.7%/23.3%
Daily steroid dose (mg/day)	3.08	1.31
Daily thyroxine dose (ug/day)	87.79	19.95

LSCS; Lower segment caesarean section, ES; empty sella

Figure 1: Basal and stimulated Copeptin levels of SS with DI (n = 4) and without DI (n = 39)

Table 2: Comparison of clinical and laboratory parameters of subjects with SS, CDI, and controls

Parameters	SS (*n*=43)	CDI (*n*=18)	Controls (*n*=19)
Age (years)	48.23±7.63	27.64±13.36[a]	38.15±10.49[bc]
BMI (kg/m^2)	24.38±4.56	24.28±5.94	25.67±4.53
SBP (mmHg)	113.95±12.25	110.56±9.98	119.47±14.2[c]
DBP (mmHg)	72.98±8.23	71.67±5.14	77.05±9.8
Urine volume/day in litres	2.47±0.53	9.44±2.53[a]	2.34±0.42[c]
Serum osmolality (mOsm/kg H$_2$O)	291.88±4.73	300.17±11.11[a]	287.34±8.34[c]
Urine osmolality (mOsm/kg H$_2$O)	482.66±141.31	168.67±44.44[a]	643.32±204.84[c]
Serum sodium (mEq/L)	143.82±4.02	147.72±2.68[a]	141.2±5.67[c]
Serum IGF1 (ng/mL)	59.73±31.35	136.03±84.83[a]	146.05±52.21[b]
Serum cortisol (µg/dL)	1.78±0.61	9.98±5.1[a]	11.82±2.63[b]
Serum T3 (ng/mL)	1.01±0.34	1.13±0.26	0.96±0.2
Serum T4 (µg/dL)	9.28±2.28	8.83±2.29	9.4±2.2
Serum TSH (µIU/mL)	0.6±0.32	4.46±3.37[a]	2.97±1.32[bc]
Serum LH (IU/L)	3.51±2.7	6.69±1.48[a]	9.19±3.33[b]
Serum FSH (IU/L)	8.9±1.82	7.9±1.45	13.42±1.98
Serum prolactin (ng/mL)	3.05±2.7	14.75±15.67[a]	10.1±8.56[b]
Serum basal copeptin (pmol/L)	26.01±12.41	1.81±0.14[a]	31.92±7.85[bc]

Values as mean±SD unless specified: $P<0.05$ is significant a=case vs. CDI, b=case vs. control, c=CDI vs. control

significant differences were noted in basal serum sodium and plasma osmolality between the two groups. However, after WDT, plasma osmolarity increased in SS patients compared to controls.[16] Furthermore, in another study that conducted WDT on 16 patients with SS and 17 healthy controls, three patients were diagnosed with CDI.[14] Similarly, Atmaca *et al.*[15] subjected 27 patients with SS and 14 controls to WDT, saline loading, and thirst perception. The osmotic threshold for thirst perception was found to be higher in patients with SS compared to controls, and eight patients were labelled as having partial CDI.

Some studies also documented impaired AVP secretion in patients with SS, but no definite conclusions can be drawn.[13,16] Though AVP is the main regulator of water balance, its routine measurement as a diagnostic tool in polyureic disorders is not a standard practice. This is largely because of preanalytical issues such as AVP being an unstable molecule, mostly attached to platelets and rapidly cleared from circulation,[23] and analytical issues related to its small size.[24] AVP is produced in the hypothalamus from pre–pro vasopressin with two other peptides, namely neurophysin II and copeptin.[19] Copeptin, a 39 amino acid glycoprotein peptide, is stable at room temperature for a week and at 4°C for at least 2 weeks. The release of copeptin directly reflects that of AVP, and the

measurement of copeptin is analogous to the measurement of C-peptide to detect endogenous insulin.[25] Measurement of serum copeptin after an overnight fast is emerging as an acceptable alternative to WDT and saline loading for diagnosis of CDI.[26] In addition, measurement of serum copeptin after dehydration, saline loading, or hypoglycaemia has superiority in diagnosing CDI,[17,27] with up to a five-fold increase in AVP after hypoglycaemia.[28] In one study, 29 patients with intact posterior pituitary function and nine with established CDI (based on WDT) who had undergone pituitary surgery were subjected to ITT. Both basal and stimulated copeptin (at 45 minutes after ITT) were significantly less in patients with confirmed CDI compared to those with intact posterior pituitary function. Copeptin levels in patients with CDI were 2.4 ± 0.5 pm/L before insulin injection with a maximum of 3.7 ± 0.7 pm/L at 45 minutes after insulin injection. A stimulated copeptin level 45 minutes after insulin injection of <4.75 pm/L is considered an optimal cut-off for the diagnosis of CDI.[18]

In the current study, we documented CDI in four patients (9.2%) (two with complete and two with partial DI) based on basal and stimulated copeptin concentrations. Two of these patients were symptomatic and needed desmopressin treatment for control of polyuria while the other two were asymptomatic. Factors such as age, parity, and duration of disease were associated with a higher possibility of DI. None of the factors such as the extent and severity of anterior pituitary hormone deficiency correlated with the presence or severity of DI.

While this study could yield valuable insights into evaluating posterior pituitary dysfunction in patients with SS, it also has some limitations to consider. The primary constraint lies in the estimation of serum copeptin using ELISA, which is associated

Table 3: Basal and stimulated copeptin levels in patients with SS and CDI

Copeptin (pmol/L)	SS without DI (n=39)	SS with DI (n=4)	CDI (n)
Basal	28.39±10.38	2.81±0.31	1.81±0.14 (18)
30 minutes	29.59±14.2	3.71±0.48	3.33±0.88 (4)
45 minutes	30.07±12.86	4.08±0.84	4.43±0.13 (4)
90 minutes	30.03±13.26	3.93±0.35	3.88±0.85 (4)

Table 4: Comparison of clinical, biochemical, and hormonal parameters of SS patients with and without CDI (based on copeptin assay)

Parameter	SS without CDI (n=39)	SS with CDI (n=4)	P
Age (years)	48.02±7.67	50.25±7.84	0.585
Duration of disease (years)	20.33±6.72	21.25±5.33	0.796
BMI (kg/m²)	24.38±4.68	24.32±3.63	0.981
Parity	3.38±1.68	4.25±1.26	0.345
Urine volume/day in litres	2.37±0.43	3.2±0.86	0.002
Serum osmolality (mOsm/kg H_2O)	291.90±4.92	291.75±2.97	0.915
Urine osmolality (mOsm/kg H_2O)	493.34±136.37	378.34±167.46	0.123
Serum sodium (mEq/L)	143.75±3.84	144.50±6.14	0.724
Serum IGF1 (ng/mL)	61.65±31.74	41.07±21.80	0.215
Serum cortisol (µg/dL)	1.79±2.66	1.12±1.15	0.627
Serum T4 (µg/dL)	9.18±2.37	8.84±2.14	0.684
Serum GH (ng/mL)	0.034±0.06	0.032±0.045	0.956
Serum LH (IU/L)	3.72±9.92	0.76±0.59	0.558
Serum FSH (IU/L)	9.50±18.27	3.52±2.69	0.521
Serum prolactin (ng/mL)	3.07±2.64	3.44±3.37	0.797
Serum basal copeptin (pmol/L)	28.39±10.38	2.81±0.31	<0.01
Serum peak copeptin (pmol/L)	30.07±12.86	4.08±0.84	<0.01

with a higher coefficient of variation. In addition, the cut-off values utilised lack thorough validation.

CONCLUSION

The study findings indicate that 9.2% of women with SS receiving hormone replacement therapy exhibit posterior pituitary dysfunction. Interestingly, only half of these individuals show symptoms such as increased urination and thirst. Utilising basal or stimulated copeptin testing could emerge as an alternative method for identifying abnormalities in AVP secretion.

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Authors' contribution

BAL: Conceptualization, writing – original draft, formal analysis, writing – review and editing, supervision; SKB: Conceptualization, writing – original draft, formal analysis, writing – review and editing. MSB: formal analysis, writing – review and editing. ZAS: writing – review and editing.

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Conflicts of interest

There are no conflicts of interest.

Data Availability statement

Authors declare that data related to the study will be made available upon request.

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