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RESEARCH ARTICLE

Comparison of self-rated pain and salivary alpha-amylase and cortisol levels during early stages of fixed orthodontic and clear aligner therapy

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ABSTRACT

Objectives: To compare self-rated orthodontic pain (OP) and whole salivary alpha-amylase (αA) and cortisol levels (CL) during early stages of fixed orthodontic and clear aligner therapy (CAT).

Methods: In groups 1 and 2, malocclusions were treated using fixed orthodontic appliances and CAT, respectively. In Group-3, individuals had normal occlusion and had never undergone orthodontic therapy. Self-rated OP was assessed using the visual-analogue-scale at baseline (T0); after 24-hours (T1) of appliance activation; and after 30 days (T2). Unstimulated whole saliva was collected and αA and CL were measured using enzyme-linked immunosorbent assay. $p < .01$ was considered statistically significant.

Results: Twenty-four (Group-1), 24(Group-2) and 25 (Group-3) patients were included. In groups 1 and 2, participants had Class-I malocclusion with anterior-crowding in both arches. At baseline (T0) none of the participants reported pain on mastication. In groups 1 ($p < .01$) and 2 ($p < .01$), OP was higher at T1 than T2. In groups 1 and 2, αA and CL were higher at T1 ($p < .01$) than T0 and T2. At T1 and T2, salivary αA and CL were higher in groups 1 ($p < .01$) and 2 ($p < .01$) than Group-3. In groups 1 and 2, a significant correlation was recorded between OP and αA ($p < .01$) and CL ($p < .01$) at T1 interval.

Conclusion: Self-rated OP and salivary αA and CL during the early stages of fixed OT and CAT are similar. Whole salivary αA and CL and OP and are high during the first 24 hours of fixed OT and CAT activation.

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Alpha amylase; clear aligner therapy; cortisol; fixed orthodontic therapy; pain; saliva

Introduction

Traditionally, orthodontic therapy (OT) encompasses the application of forces to dentoalveolar tissues using fixed appliances such as brackets and archwires. During orthodontic tooth movement (OTM), a cascade of biologic events such as vascular changes, recruitment of inflammatory cells and release of inflammatory cytokines are activated that induce OTM [1]. Active orthodontic forces often induce pain (also known as orthodontic pain [OP]), which patients perceive as sore teeth and/or pressure/tension in teeth [2–5]. The prevalence of orthodontic pain (OP) ranges between 72% and 100% [3–5]. Studies [6–9] have shown that OP usually initiates 12-hours after activation of orthodontic forces, mounts after 24-hours, and progressively diminishes after three to seven days and reverts to baseline-levels after 30 days. Although OT using fixed appliances is a reliable and predictable treatment strategy; it is often challenging for patients to maintain routine oral hygiene. Moreover, some individuals consider fixed orthodontic appliances such as metal wires and brackets unacceptable and esthetically displeasing [10–12]. With advancements in clinical orthodontics and related research, clear aligner therapy (CAT) has emerged as an attractive and esthetically acceptable substitute to fixed OT for the management of dental malocclusions including Class-I malocclusion with anterior crowding [13–16]. With regards to pain, Gao et al. [17] showed that patients treated with CAT perceive OP to a much lesser extent compared with patients undergoing fixed OT. It has also been suggested that oral health-related quality of life (OHRQOL) is superior in patients undergoing CAT than fixed OT [18–20].

It has been reported that OP-related stressful episodes increase enzymatic and hormonal activity in whole saliva [19–21]. Alpha amylase (αA) is an enzyme that predominantly hydrolyzes glycogen and starch [22]; however, OP induced-stress has also been reported to increase salivary αA activity [21,23]. Likewise, cortisol is a stress hormone that is expressed in raised concentrations in biological fluids (including whole saliva) during oral inflammatory conditions and episodes of anxiety and pain [24,25]. A limited number of clinical studies [19,25] have assessed self-rated pain using the visual analog scale (VAS) and salivary stress biomarkers (such as αA and cortisol levels [CL]) during initial phases of fixed OT. According to Silva Andrade et al. [20] and Aksoy et al. [19] OP is associated with emotional stress, which increases

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salivary αA and CL, respectively during initial alignment phase of fixed OT. However, no studies have investigated OP and salivary αA and CL during initial alignment phase in individuals undergoing CAT and fixed OT.

The purpose was to evaluate self-rated OP and salivary αA and CL during early stages of fixed orthodontic and CAT. The *null* hypothesis is that there is no difference in the self-rated pain and salivary αA and CL during early stages of fixed orthodontic and CAT.

Material and methods

Ethical approval

The research study was reviewed and approved by the Ethical Committee of Health Sciences Center at Kuwait University, (VDR/EC-4069). Participation was completely voluntary and withdrawal at any stage did not bear any penalty and/or consequence. It was mandatory for patients to read and sign a written informed consent form. Declaration of Helsinki guidelines were followed in the present study.

Eligibility criteria

Inclusion criteria were: (a) Patients with dental malocclusions seeking OT; (b) patients scheduled for OT using fixed orthodontic appliances; (c) patients scheduled for OT using CAT; and (d) individuals with a normal occlusion not seeking any type of OT (controls). Exclusion criteria were: (a) denial to signing the informed consent; (b) patients with skeletal malocclusions; (c) patients requiring extraction of teeth and/or surgical craniofacial interventions prior to OT; and (d) patients with a history of OT. Moreover, patients with a self-reported history of oral diseases (such as periodontitis) and systemic conditions including cancer, psychological diseases including anxiety/depression, prediabetes and diabetes mellitus; and individuals that reported to have used NSAIDs, anti-biotics and/or steroids within 90 days were excluded.

Grouping

Based upon the method used to achieve OTM, patients were divided into two groups. In Group-1, patients were undergoing OT using fixed orthodontic appliances using 0.016 × 0.016 arch-wires (NIC NiTi, ROS31L0016, WI, USA) and brackets (3B Orthodontic Machining Brackets, NY, USA). In Group-2, CAT (Align Tech. Invisalign®, CA, USA) was performed for the correction of malocclusion. Group-3 comprised individuals that reported to have never undergone OT using fixed/removable appliances and had normal occlusion [26].

Assessment of dental records

The following parameters (a) sex; (b) age; (c) type of malocclusion; (d) type of orthodontic treatment (fixed OT or CAT); (e) self-reported oral and systemic health status was retrieved from dental records.

Allocation concealment and blinding

Based upon the nature of the present study; it was challenging to conceal the groups to which, participants were allocated. However, αA, CL, and statistical tests were performed by investigators who were blinded to the study groups.

Collection of whole saliva samples

Unstimulated whole saliva was collected as described elsewhere [27]. In brief, fasting whole saliva was collected by a calibrated investigator (*Kappa* score 0.88) with patients seated on a chair. Patients allowed saliva to accumulate in the mouth for five minutes and during this time did not swallow or move their jaw. The saliva was expectorated into a measuring cylinder and salivary flow rate was measured. After this, each saliva sample was placed to sterile plastic tubes and the lid was sealed (Salivette™, Sarstedt Inc., Numbrecht, Germany). The supernatant was collected by vortexing the tubes at 1500 × g for five continuous minutes. The supernatant was stored at −70 °C and assessed for CL and αA levels within 24-hours.

Assessment of alpha-amylase and cortisol levels

The αA was measured according to the protocol described in previous studies [20,28]. In summary, a commercially available salivary αA enzymatic assay kit (RE80111, IBL International GmbH, D-22335 Hamburg, Germany) was used according to the manufacturer's instructions. The Salivary CL was assessed by a kinetic-enzymatic method for salivary amylase using a commercial assay kit (Salimetrics™, Carlsbad, CA, USA). For both kits, samples were assessed in triplicate and absorbance was read at 405 nm using a spectrophotometer (Biomate 3, Thermo Fisher Scientific, Waltham, MA, USA)

Time intervals

In all groups, unstimulated whole saliva samples were collected; and αA and CL were assessed at the following time intervals: (a) pretreatment phase/baseline (T0); (b) after 24-hours (T1) of appliance activation; and (c) after 30 days (T2).

Assessment of self-rated pain

The VAS [29] was used for quantification of self-rated pain on mastication. Self-rated pain was assessed at the following time intervals: (a) pretreatment phase/baseline (T0); (b) after 24-hours (T1) of appliance activation; and (c) after 30 days (T2) by a calibrated examiner (*Kappa* score 0.82).

Power and statistical analyses

Power analysis was done using a computer-based program (*n*Query Advisor-6, Statistical Solutions, MA, USA) using preliminary data obtained from a pilot study with 10 individuals per group. It was estimated that at least 22 individuals would be needed in each group in order to detect a 2 cm difference

in VAS with an alpha of 1%. The study power was 90%. Commercial software (IBM, SPSS Version 22, Chicago, IL, United States) was used to perform quantitative analyses. Kolmogorov-Smirnov test was used to test data-normality; and one-way analysis of variance and Bonferroni *Post-hoc* tests were done to compare self-rated pain and salivary αA and CL among groups. Correlation between self-rated pain and age, gender and salivary αA and CL were assessed using logistic regression models. P-values, which were below .01 were considered statistically significant.

Results

Patient population

Twenty-four (Group-1),24 (Group-2) and 25 (Group-3) patients volunteered to participate. In groups 1, 2 and 3, 14, 16 and 15 participants were males. Mean ages of subjects in groups 1,2 and 3 were 29.2 ± 2.5, 31.07 ± 1.6 and 26.6 ± 0.5 years, correspondingly (Table 1). In groups 1 and 2, participants had Class-1 malocclusion with anterior crowding in both arches. Mean salivary flow rate in groups 1, 2, and 3 were 0.11 ± 0.08 ml/min, 0.11 ± 0.1 ml/min and 0.11 ± 0.1 ml/min

Salivary cortisol and alpha-amylase levels

Intra-group comparisons

In groups 1 and 2, salivary αA and CL were significantly higher at T1 ($p < .01$) interval compared with T0 and T2. No significant difference was detected in αA and CL at T1 and T2 intervals in groups 1 and 2. In Group-3, there was no difference in αA and CL at all time intervals (Table 2). In groups 1 and 2, there was a statistically significant correlation between self-rated pain and salivary αA ($p < .01$) and CL ($p < .01$) at T1 interval. At T2 interval, there was no significant association between self-rated pain and salivary αA and CL in groups 1 and 2 (Figures 1 and 2).

Table 1. Characteristics of the study groups.

Variables	Group-1	Group-2	Group-3
Number of patients	24	24	25
Male: Female	14 : 10	16 : 8	15 : 10
Age in years	29.2 ± 2.5 years	31.07 ± 1.6 years	26.6 ± 0.5 years

Group-1: Fixed orthodontic treatment.
Group-2: Clear aligner therapy.
Group-3: Patients with normal occlusion (Controls).
NA: Not applicable.

Intergroup comparisons

At baseline (T0), salivary αA and CL were comparable in all groups. At T1 and T2 intervals, mean salivary αA and CL were significantly higher in groups 1 ($p < .01$) and 2 ($p < .01$) compared with Group-3. There was no significant difference in the mean salivary αA and CL at T1 and T2 intervals in groups 1 and 2 (Table 2). There was no statistically significant correlation between age ($p = 0.17$), gender ($p = 0.15$), and salivary αA ($p = 0.12$) and CL ($p = 0.15$) at T1 and T2 intervals in groups 1 and 2 (data not shown).

Self-rated pain levels on chewing

At baseline (T0) none of the participants reported pain on mastication. In groups 1 ($p < .01$) and 2 ($p < .01$), self-rated pain scores were significantly higher at T1 compared with T2. When self-rated pain scores were compared between groups 1 and 2 at T1 and T2 intervals, no statistically significant difference was noted. In Group-3, self-rated pain was found in none of the participants (Table 3).

Discussion

The present study outcomes are in accordance with the *null* hypothesis. With respect to self-rated OP scores, our results, based on mean scores from the VAS showed that self-rated OP levels were comparable in groups 1 and 2 at T1 and T2 intervals. In other words, there was no significant difference in self-rated OP during initial aligning phase in groups 1 and 2. These results are in contradiction to those reported in a systematic review in which, Cardoso et al. [30] evaluated differences in OP levels among patients undergoing CAT and fixed OT. According to results of this systematic review [30], patients undergoing CAT perceive OP to a much lesser extent compared with individuals undergoing fixed OT. We perceive those results by Cardoso et al. [30] should be cautiously interpreted as a number of factors may have influenced the outcomes. Firstly, there was an inconsistency in the designs of the seven studies that were systematically reviewed (five non-randomized clinical trials, one cross-sectional study and one randomized conical trial) [30]. Moreover at least 71% studies evaluated in this systematic review had a moderate risk of bias. Furthermore, quantitative evaluation (meta-analysis) was not performed on the studies included in this systematic review. In the present study, the type of malocclusion under treatment was standardized (Class-I malocclusion). It is notable that there was no stringent criterion to

Table 2. Salivary alpha-amylase and cortisol levels in groups 1, 2 and 3 at baseline (T0), and after 24-hours (T1) and 30 days (T2).

	Group-1			Group-2			Group-3		
Variables	T0	T1	T2	T0	T1	T2	T0	T1	T2
Alpha amylase levels (U/ml)	12.4 ± 9.3 U/ml	42.7 ± 8.5 U/ml[a]	26.3 ± 6.5 U/ml	10.6 ± 5.1 U/ml	37.5 ± 6.4 U/ml[b]	21.4 ± 5.3 U/ml	12.4 ± 4.6 U/ml	11.4 ± 2.4 U/ml	14.4 ± 5.3 U/ml
Cortisol levels (mg/ml)	1.21 ± 0.8 ng/ml	5.63 ± 0.4 mg/ml[a]	4.88 ± 0.7 ng/ml	1.42 ± 0.3 ng/ml	4.87 ± 0.5[b] ng/ml	2.3 ± 0.08 ng/ml	2.02 ± 0.05 ng/ml	1.87 ± 0.07 ng/ml	1.74 ± 0.1 ng/ml

[a]Compared with T0 ($p < .01$) in Group-1.
[b]Compared with T0 ($p < .01$) and T2 ($p < .01$) in Group-2.
Group-1: Fixed orthodontic treatment.
Group-2: Clear aligner therapy.
Group-3: Patients with normal occlusion (Controls).

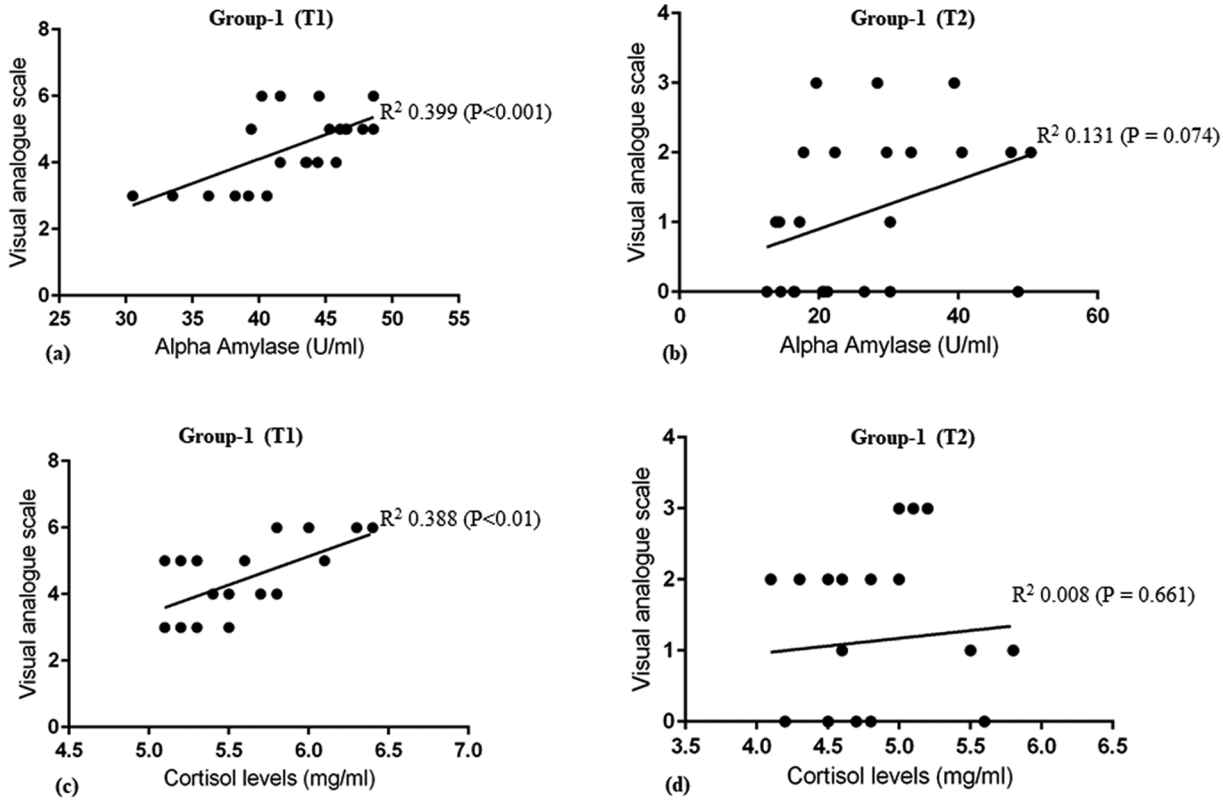

Figure 1. Group 1 at T1 and T2 intervals, correlation between self-rated pain and salivary Alpha Amylase and Cortisol Level.

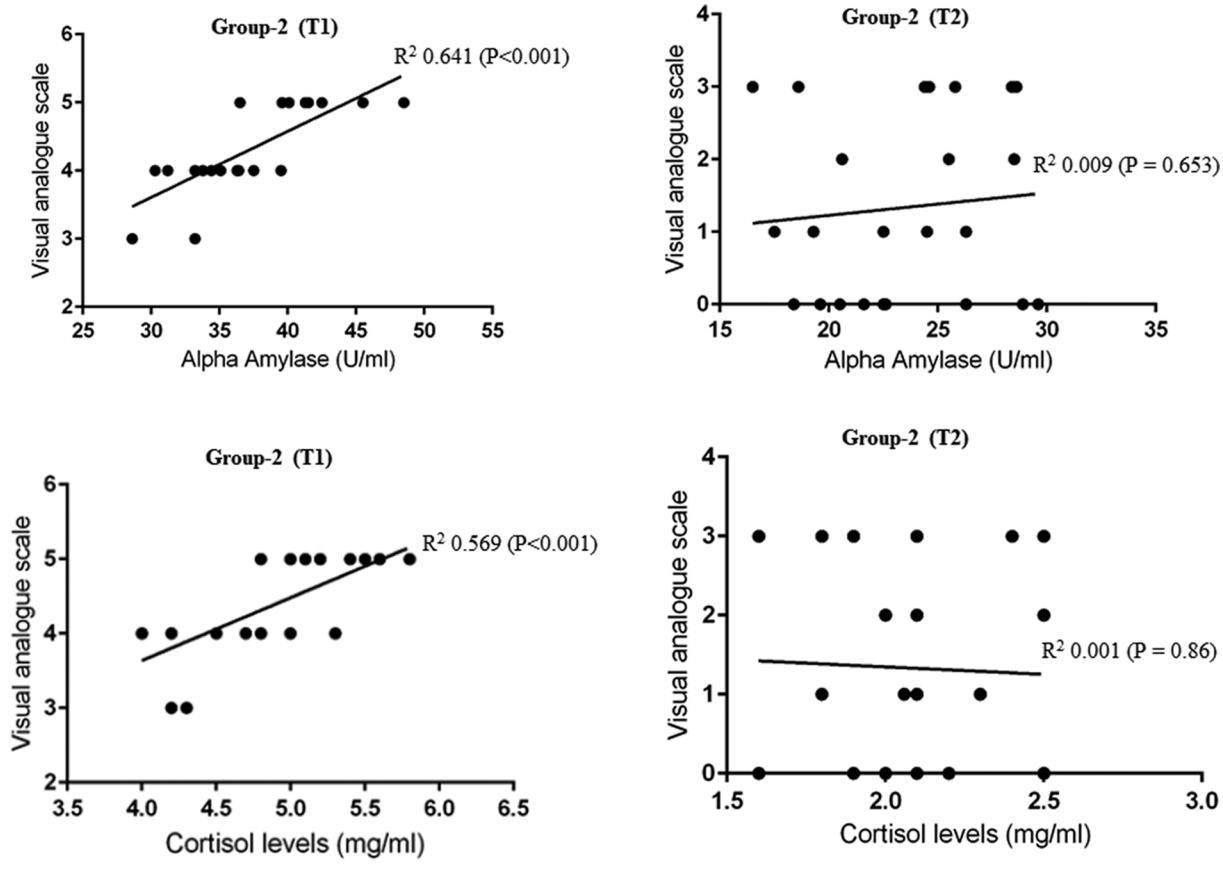

Figure 2. Group 2 at T1 and T2 intervals, correlation between self-rated pain and salivary Alpha Amylase and Cortisol Level.

Table 3. Self-rated pain scores on chewing at T1 and T2 intervals.

	Group-1		Group-2		Group-3	
Variables	T1	T2	T1	T2	T1	T2
Self-rated pain scores	4.5 ± 0.08[a]	1.1 ± 0.03	4.3 ± 0.1[b]	1.3 ± 0.05	0	0

[a]Compared with T2 in Group-1 ($p < .01$).
[b]Compared with T2 in Group-2 ($p < .01$).

include patients with Class-I malocclusions only in the current investigation; however, patients that consented to participate in our study had Class-I malocclusion with crowding in the anterior sextant. The authors applaud results of a study [31] in which, Class-I malocclusions were reported as most prevalent (74.7%) dental misalignments in permanent dentition followed by Class-II (19.6%) and -III (5.9%) on a global perspective.

Presently, two clinical studies [19,20] have assessed whole salivary αA and CL in order to determine OP-induced stress levels during initial phase of orthodontic force application. It is notable that at T1 interval, patients in groups 1 and 2 demonstrated significantly higher αA and CL compared with their respective T0 values (Table 2). Moreover, the mean VAS scores were also comparable in groups 1 and 2 at T2 interval (Table 3). These results are in conflict with those reported in a recent study [17] according to which, self-rated OP scores are higher in patients undergoing fixed OP in contrast to patients receiving CAT for correction of malocclusion. We found no difference in OP scores in groups 1 and 2 and from the authors' point of view significantly high αA and CL in groups 1 and 2 (with regards to their corresponding T0 values) validates our results. However, one aspect in which, we appraise Gao et al. (2021) is that the OP levels escalated after 24 h of orthodontic force application in groups 1 and 2 and significantly reduced at T2 interval in both groups. A critical assessment of the study by Gao et al. (2021) showed that the reported p-values were based on a study sample that was not previously power adjusted. In addition, random patient grouping was unfeasible in the study by Gao et al. (2021) are potential factors that could have biased the results reported by Gao et al. (2021). The present logistic regression analysis results showed a statistically significant correlation between self-rated OP scores and whole salivary αA and CL in both groups at T1 interval. One clear justification for this is that T1 was the time frame during which orthodontic forces were initially activated in groups 1 and 2; and this could have induced a state of psychological stress or anxiety in groups 1 and 2. Our results also showed that as the self-rated OP scores reduce (T2 interval), their correlation with salivary αA and CL also weakens from a statistical standpoint. Therefore, whole salivary αA and CL could be potential biomarkers of self-rated pain particularly in patients with a low pain tolerance. Nevertheless, further studies are needed to test this hypothesis.

Despite the present study sample being power-adjusted a major limitation is that the levels of anxiety and OHRQOL of patients in all groups were not assessed. It has been reported that the state-trait anxiety inventory and oral health impact profile-14 are valid and reliable tools for the assessment of perceived anxiety and OHRQOL [32–34]. Moreover, an underprivileged socioeconomic status (SES) has also been associated with poor self-rated pain tolerance [35]. This parameter remained uninvestigated in the present patient population. Additional studies are therefore needed to vigorously evaluate the effects of CAT on levels OP with emphasis on patients' stress and anxiety levels, SES and their OHRQOL. In conclusion, self-rated OP and salivary αA and CL during early stages of fixed OT and CAT are similar. Levels of self-rated OP and whole salivary αA and CL are high during the first 24-hours of fixed OT and CAT activation.

Authors' contributions

DA: Conceptualization, Supervision, Methodology, Software, Original draft preparation, Reviewing and Editing. DA and HA: Data curation, Literature search, Writing- Original draft preparation, Reviewing and Editing. DA, HA, and MA: Quantitative analysis; DA, HA, and MA: Writing-Original draft preparation Visualization, Writing- Reviewing and Editing, Writing- Reviewing and Editing. DA, HA, and MA: Methodology, Original draft preparation. DA, HA, and MA: Original draft preparation and revision of manuscript prior to submission, Writing- Reviewing and Editing.

Disclosure statement

The authors declare that they have no conflict of interest.

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Data availability statement

Data supporting the findings of the present study is available upon reasonable request.

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