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Genetic variants of vitamin-D receptor genome and teeth caries susceptibility in Iraqi children

Variantes genéticas do genoma do recetor de vitamina D e suscetibilidade à cárie dentária em crianças iraquianas

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ABSTRACT

Objective: To find out if there is a link between the TaqI, ApaI, BsmI, and FokI polymorphisms of the vitamin D receptor (VDR) and dental caries risk in Iraqi children. **Material and Methods:** The study had a sample of one hundred children, consisting of fifty males and fifty females, their mean age of 10.2 ± 1.21 years old. The study volunteers were categorized into two groups: a moderate caries risk group (DMFT, 1-4) consisting of 50 individuals, and a caries-free group including 50 individuals. Salivary samples were obtained from each participant, and subsequent DNA extraction was performed. The VDR gene was geno-typed using the polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) techniques. All data were subjected to statistical analysis using the chi square test, Fisher's exact test, and Odds ratios; results considered significant when ($P<0.05$). **Results:** A statistically significant difference was seen in the frequency of FokI genotypes (CC) between children with caries and those without caries ($P<0.05$). Individuals possessing the (CC) genotype had a 2.745-fold higher probability of being susceptible to dental caries with CI 95% of (1.077 - 6.996). While there were no significant differences ($P>0.05$) found between the TaqI, ApaI, and BsmI genotypes and cavities in the teeth. **Conclusion:** FokI (rs2228570) polymorphisms of the vitamin D receptor (VDR) showed an association with dental caries. VDR genetic variants may be employed in the future as a potential marker for identifying people at risk for caries when paired with environmental variables, as well as for caries prevention and treatment.

KEYWORDS

Caries; Gene; Genetic; Polymorphism; Vitamin D.

RESUMO

Objetivo: Descobrir se existe uma ligação entre os polimorfismos TaqI, ApaI, BsmI e FokI do recetor da vitamina D (VDR) e o risco de cárie dentária em crianças iraquianas. **Material e Métodos:** O estudo teve uma amostra de cem crianças, composta por cinquenta do sexo masculino e cinquenta do sexo feminino, com uma idade média de 10,2 ± 1,21 anos. Os voluntários do estudo foram categorizados em dois grupos: um grupo de risco moderado de cárie (CPO-D, 1-4), constituído por 50 indivíduos, e um grupo sem cárie, constituído por 50 indivíduos. Foram obtidas amostras salivares de cada participante e subsequente extração de DNA. O gene VDR foi genotipado utilizando a reação em cadeia da polimerase (PCR) e técnicas de polimorfismo de comprimento de fragmentos de restrição (RFLP). Todos os dados foram submetidos a análise estatística utilizando o teste do qui-quadrado, o teste exato de Fisher e Odds ratios; os resultados foram considerados significativos ($P<0,05$). **Resultados**: Foi observada uma diferença estatisticamente significativa na frequência dos genótipos FokI (CC) entre crianças com cárie e sem cárie ($P<0,05$). Os indivíduos que possuíam o genótipo (CC) tinham uma probabilidade 2,745 vezes maior de serem susceptíveis à cárie dentária com IC 95% de (1,077 - 6,996). Embora não tenham sido encontradas diferenças significativas ($P>0,05$) entre os genótipos TaqI, ApaI e BsmI e as lesões de cárie nos dentes.

Conclusão: Os polimorfismos FokI (rs2228570) do recetor da vitamina D (VDR) mostraram uma associação com a cárie dentária. As variantes genéticas do VDR podem ser utilizadas no futuro como um potencial marcador para a identificação de pessoas em risco de cárie quando emparelhadas com variáveis ambientais, bem como para a prevenção e tratamento da cárie.

PALAVRAS-CHAVE

Cárie; Gene; Genética; Polimorfismo; Vitamina D.

INTRODUCTION

Dental decay is classified by World Health Organization (WHO) as the ternary most detrimental ailment to human well-being, right after cancer and cardiovascular disease. Based on these findings, the decayed-missing-filled index has exhibited a global drop due to advancements in the field of stomatology. However, it is important to note that dental caries continues to adversely affects the physical characteristics and overall well-being of a significant proportion of school-aged children, ranging from 60% to 90%, as well as most adults [1].

Vitamin D has been recognized as a risk factor for the occurrence and prevalence of dental caries due to its involvement in two significant roles. It plays an essential function in the oral cavity, especially in the mineralization of teeth and antibacterial action through the stimulation of antibacterial peptide secretion, as well as its influence on “ameloblasts and odontoblasts” cells in the creation of enamel and dentin via the signaling pathways [2]. It is currently understood that Vitamin D Receptor (VDR) in many cells throughout the body, including those in salivary gland, dentin and enamel forming cells. The binding of vitamin D to its VDR, which is a nuclear transcription factor, influences the activity of various genes that make up about 5-10% of the human genome. These genes are involved in mineral metabolism, cell life cycle, immune response, and energy metabolism, resulting in genomic effects [3].

Vitamin D receptor is a ligand-dependent transcription modulator which maps to human chromosome 12q13.1; that facilitates 1,25 (OH)2 D3’s cytoplasmic distribution. Its binding to the vitamin D receptor element enables it to carry out several functions, such as immune cell charatarization, bone mineralization, improved homeostasis, its important in regulating calcium and phosphorus metabolism, as well as cell growth and differentiation. The biological functionality of 1,25-dihydroxyvitamin D3 is determined by its interaction with the ligand-activated transcription factor [4].

Polymorphism refers to genetic variations that occur in 1% or more of the population. Some of these genetic variables produce or eliminate restriction enzyme positions in DNA [5]. Thus, restriction enzyme-digestion of DNA containing these variants results in DNA fragments of varying lengths and sizes, and these polymorphisms are referred to as restriction fragment length polymorphisms (RFLPs). The presence of single nucleotide polymorphisms within the VDR gene has been observed to have an impact on the Taq-1, Apa-1, and Bsm-1 sites located in exons 8 and 9. Additionally, the Fok-1 site is influenced by a specific polymorphism that is situated within exon 2 [6]. There is a growing body of evidence suggests that hereditary elements may be associated with caries susceptibility, and genetic factors account for over 40% of caries risk [7]. Identifying the susceptibility of the host, i.e., the role of diverse genetic elements, improves the willingness of specialist to clarify the significance of family history and hereditary risk indicators in the development of disease [8]. Controlling caries will require the development of new methods for identifying those who are at a high risk. As observed in the previous studies, host genetic variation, such as the Vitamin D Receptor (VDR), may play a role in elevating the susceptibility to the disease. Therefore, it is crucial to investigate VDR gene polymorphisms as a marker for identifying patients who are at a high risk of developing caries [9,10]. A recently published comprehensive study confirms that there is a greater incidence of dental caries in individuals with low levels of vitamin D, however the connection with VDR gene receptors is still uncertain. More investigations are required to fully understand the complex relationship between dental caries and vitamin D and its receptor [11].

Here, we investigated in this case control-study the relationship between polymophisms

in the VDR domain and its association with predisposition to dental caries in salivary samples of Iraqi children, using (RFLPs).

MATERIALS AND METHODS

Study Subjects: The study included a sample of 100 children, with age range (8 to 10 years), who needed dental care at the pedodontics and preventive department of Mustansyriah University's College of Dentistry. The children selection was based on specific criteria, mixed dentition (primary and permanent) according to the age sample (8-10) which involved experiencing pain due to caries or seeking routine dental checkups. The participants exhibited a state of good health, as they did not present any systemic disorders and were not consuming any nutritional supplements. The participants were given a sheet of information that described every aspect of the study and the use of saliva samples. Saliva samples were taken subsequent to an oral examination. In addition, the DMFT (D: decayed, M: missing, F: filled, T: tooth for permanent teeth) and dmft (d: decayed, m: missing, f: filled, t: tooth for deciduous teeth) indices were recorded according to WHO criteria 1997 [12] and all children were classified according to the DMFT scores into:

Group-1 (Control group): caries-free (dmft/DMFT=0): This group consists of individuals who have no dental caries, no teeth missing due to caries, and no fillings. A DMFT score of 0 indicates that the person has not experienced any tooth decay or required any restorative dental treatments. This group represents the baseline or ideal oral health status in the study.

Group-2 (Patients group): with moderate caries (dmft/DMFT=1-4): This group includes individuals who have a DMFT score ranging from 1 to 4. This means they have experienced one to four instances of dental caries, missing teeth due to caries, or filled teeth. The DMFT index of 1-4 indicates a moderate level of caries risk, signifying some degree of dental health issues but not severe enough to be classified as high risk (which would typically have a higher DMFT score).

Ethical aspect of the study

The study was authorized by Mustansiriyah University's Ethics committee with REC reference REC131, study number MUPREV202301; and according to the principles of the Declaration of Helsinki. Subjects' rights have been protected after receiving written informed consent from the parents of the children to use their information's and saliva for dental research purposes.

Sample Size was calculated at 95% confidence interval with a 5% error margin using the online program EPITOOLS (https;//epitools.ausvet.com.au/casecontrolss).

Name, age, residence, and habits have all been requested for each patient. All individuals had identical environmental exposures.

In the dental clinic, examinations were carried out on dental chairs, using dental mirrors and sharp dental explorers. The examinations of occlusal and interproximal surfaces of the teeth were carried out under artificial lights. Teeth that were decayed, missing, due to caries, or filled were recorded according to the modified World Health Organization 1997 caries diagnostic criteria. The Numbering System approach was used to examine the teeth. Starting with the last upper right molar, the examination proceeded in a systematic manner from one tooth to the next neighboring tooth until the upper left last molar was reached. Next, the lower left last molar was examined, followed by the lower last right molar. The process was repeated until all the teeth in the mouth had been examined. Caries examination and diagnosis were performed by two dentists, and examination consistency was certified by examining 30 children before the initiation of the study.

Saliva Sample Collection: Saliva samples that had not been stimulated were obtained by following the steps outlined in the Navazesh protocol [13]. Before the sample collection, the participants were instructed to avoid brushing; abstain from eating and drinking for a period of two hours. The samples were taken between the hours of 10:00 and 11:00 in the morning. In order to keep the participants relaxed and stress-free during the whole process of collecting samples, a regular chair was used instead of a

dental chair to seat them. After the un-stimulated saliva had accumulated in the mouths floor, a volume of 5 milliliters was taken and placed in the saliva collecting tube. The samples of saliva were centrifuged, and the supernatant that was produced was chilled to a temperature of - 4°C for further analysis.

Salivary DNA Isolation: Salivary DNA was isolated according to the manufacturer's instructions utilizing a reagent that is commercially-available (Salivary DNA Isolation reagent, Norgen \ Biotek, Canada)). The DNA quantity in each sample was measured by a spectrophotometer and afterwards kept at a temperature of -20°C until further analysis was conducted.

Single Nucleotide Polymorphism Selection and Geno-typing: The VDR SNP was chosen after reviewing the literature and retrieved from NCBI "(https://www.ncbi.nlm.nih.gov)". To determine the RFLP, the amplification of DNA was achieved using polymerase chain reaction (PCR) technique, followed by digestion with a specific restriction enzyme. The following primer pairs are listed in (Table I) for amplifying the DNA flanking of SNPs.

PCR (RFLPs) assay

The PCR mixture, with a volume of 25 μl, was composed of various components. These included 10mM TrisHCl, 200 μM dNTPs, 20 pmol of each primer, 1.5mM MgCl2, 0.5 units of Taq polymerase (F enzyme) and 50 to 100 nanograms of DNA to use as a template. The cyclic pattern can be described as follows: The thermal cycling procedure encompassed an initial denaturation stage at a temperature of 94°C for a duration of 5 minutes, continued by 35 cycles of amplification. The experimental procedure involved a series of cycles, with each cycle including a denaturation phase at 95°C heating for 60 seconds, followed by an annealing step at 68°C for 60 seconds, and with an extension step at 72°C for a period of 2 minutes. The final extension step for 7 minutes was performed at 72°C. A 10 microliter amount of the polymerase chain reaction (PCR)-amplified product was submitted to enzymatic digestion using restriction enzymes at a temperature of 37°C for an overnight duration. The digested product was then brought into view by running it on an ethidium bromide-stained 3% agarose gel.

Statistical Analysis

The study results presented using several statistical measures, such as frequency (expressed as a percentage), mean, and standard deviation. The chi-square test, variance analysis, and t-test were utilized for making comparisons. Odds ratios and 95% confidence intervals (CIs) were calculated. The p-value for Hardy-Weinberg equilibrium (HWE) was assessed using the chi-squared test, $P< 0.05$ was considered a significant divergence from HWE.

Statistical comparisons were conducted using SPSS software (version 23; IBM SPSS Corp, Armonk, NY, USA).

RESULTS

The average age of the study participants was 10.2 1.21 years. The control group consisted of children with no evidence of caries (DMFT = 0; n = 50; 25 boys and 25 girls), whereas the patient group consisted of children with intermediate caries risk (DMFT = 1-4; n = 25 boys and 25 girls).

The distribution of genotypes at four polymorphic loci in selected genes among caries-free subjects and patients with caries is shown in (Table II).

In order to show the significance of the association between various SNP genotypes and caries status in the case and control groups, odds ratios were calculated too.

Table I - Primers for VDR Gene Polymorphisms

VDR SNPs	Primers
Taq-I (rs 731236) exon 9 (T > C)	F: "5- CAG AGC ATG GAG AGG GAG CAAG-3" R: "5- GGA TGT ACG TCT GCA GTG TG -3"
Apa-I (rs 7975232) intron 8 (G > T)	F: "5- CAG AGC ATG GAC AGG GAG CAAG-3" R: "5-CAC TTC GAG CAC AAGGG CGTTAG-3"
Bsm-I (rs 1544410) intron 8 (G>A)	F: "5-CAA CCA AGA CTA CAA GTA CCG CGT CATGA -3" R: "5- AAC CAG CGG GAA GAG GTC AAG GG -3"
FOK-I (rs 2228570) exon 2 (T > C) (rs 10735810) 2 SNPs	F: "5- AGC TGG CCC TGG CAC TGA CTC TGG CTC -3" R:"3- ATG GAA ACA CCT TGC TTC TTC TTC TTC CTC-5"

The genotype CC of (rs**2228570)** demonstrated a significant association with tooth decay (P = 0.027), indicating that individuals with this genotype had a 2.745-fold higher risk of active caries (OR = 2.745 95% CI = [1.077 - 6.996]).

On the other hand, the VDR polymorphisms ApaI, TaqI, and BsmI were found to have no significant association with tooth decay. The odds ratios (OR) and corresponding 95% confidence intervals (CI) for ApaI, TaqI, and BsmI were as follows: ApaI (OR = 0.419, 95% CI = [0.157 - 1.118], p = 0.051), TaqI (OR = 0.592, 95% CI = [0.224 - 1.564], p = 0.548), and BsmI (OR = 0.635, 95% CI = [0.239 - 1.685], p = 0.680), as shown in Table II.

The C and T allele frequencies of FokI and ApaI polymorphisms were substantially different between caries-experienced and caries-free groups (p = 0.005, 0.047, respectively). Interestingly FokI have a 2.7-fold increased likelihood of developing active caries (odd ratio = 2.745, with a 95% confidence interval = 1.077 - 6.996, P-value = 0.026).

Whereas no significant differences were seen in the genotypes and allele frequencies of TaqI and BsmI polymorphisms between persons with dental caries and those without dental caries. (Table III).

All the VDR SNPs were not in Hardy-Weinberg equilibrium in unaffected and affected individuals, except for rs **7975232** (ApaI) in patients' group (P=0.077) and rs **1544410 (**BsmI) in control group (P=0,064) were in agreement with HWE (Table IV).

DISCUSSION

Based on earlier research, the development of dental caries has been linked to a variety of variables. Genetic factors may play a significant role in the multifactorial character of dental caries, although their involvement in caries development has not been well investigated [14].

Dental caries can be caused by a complicated combination of heredity and environmental factors [15]. Furthermore, it has been determined that hereditary factors contribute to almost 40% of the overall risk associated with caries development [16]. Based on the findings of published studies, the risk of dental caries can be influenced by both genetic and environmental factors. These environmental factors include oral hygiene, diet, bacteria, and host factors [17,18].

Vitamin D has a crucial role in maintaining calcium homeostasis, as well as modulating the immunological response and exerting anti-inflammatory effects [19]. The VDR gene facilitates the physiological role of the vitamin D metabolite, which is linked to the regular growth of tooth enamel [20,21]. Genetic variations in the vitamin D receptor (VDR) within people have been found to result in defects and morphological diversity in tooth enamel [22].

In the present case-control research, we aim to determine the potential connection between four VDR gene variants (TaqI, ApaI, BsmI,

Table II - Genotype Distribution of Four VDR Polymorphisms in Study Groups

Genotype		Caries group No.50	Control group No. 50	Odd ratio 95% CI	*X^2	P- Value
ApaI (rs 7975232) G>T	GG	21 (42%)	16 (32%)	Referent	-	-
	GT	18 (36%)	14(28%)	0.979(0.377 - 2.544)	0.735	0.391^{NS}
	TT	11 (22%)	20(40%)	0.419(0.157 - 1.118)	3.786	0.051^{NS}
TaqI (rs731236) T>C	TT	15 (30%)	10 (20%)	Referent	-	-
	TC	11(22%)	13(26%)	0.564 (0.181- 1.752)	0.219	0.639^{NS}
	CC	24 (48%)	27(54%)	0.592 (0.224-1.564)	0.360	0.548^{NS}
FOKI (rs 2228570) T>C	TT	12 (24%)	20 (40%)	Referent	-	-
	TC	10 (20%)	13(26%)	1.282(0.430-3.819)	0.508	0.475^{NS}
	CC	28 (56%)	17(34%)	2.745(1.077 - 6.996)	4.888	0.027^{S}
BsmI (rs 1544410) G>A	GG	17(34%)	12 (24%)	Referent	-	-
	GA	15(30%)	18(36%)	0.588(0.214- 1.611)	0.407	0.523^{NS}
	AA	18(36%)	20(40%)	0.635(0.239 - 1.685)	0.169	0.680 ^{NS}

No: Number. *chi-squared test. $^{S:}$ Significant. $^{NS:}$ Non-Significant.

Table III - Allele Frequency of Four VDR Polymorphisms among Study Groups

Allele Frequency		Caries group No.50	Control group No. 50	Odd ratio 95% CI	*X^2	P- Value
ApaI (rs 7975232) G>T	G	60 (60%)	46(46%)	Referent	-	-
	T	40 (40%)	54 (54%)	0.5679(0.324 -0.995)	3.934	0.047[S]
	Total	100	100			
TaqI (rs731236)T>C	T	41 (41%)	33(33%)	Referent	-	-
	C	59 (59%)	67(67%)	0.708(0.398 - 1.261)	1.3728	0.241[NS]
	Total	100	100			
FOKI (rs 2228570) T>C	T	34 (34%)	53(53%)	Referent	-	-
	C	66 (66%)	47(47%)	2.189(1.237- 3.872)	7.735	0.005[S]
	Total	100	100			
BsmI (rs 1544410) G>A	G	49(49%)	42(42%)	Referent	-	-
	A	51(51%)	58(58%)	0.753(0.431- 1.316)	0.988	0.320[NS]
	Total	100	100			

[S]: Significant. [NS]: Non-Significant. *: Chi-squared test.

Table IV - Hardy-Weinberg equilibrium for VDR polymorphisms

VDR SNPs	HWE	Caries group No.50	Control group No. 50
ApaI (rs 7975232)G>T	HWE X^2 value	3.125	9.521
	P value	0.077 [NS]	0.002[S]
TaqI (rs731236)T>C	HWE X^2 value	14.865	8.488
	P value	0.0001[S]	0.0035[S]
FOKI (rs 2228570) T>C	HWE X^2 value	15.366	11.429
	P value	0.0000[HS]	0.0007[HS]
BsmI (rs1544410) G>A	HWE X^2 value	7.990	3.408
	P value	0.004 [S]	0.064 [NS]

[S]: Significant. NS: Non-Significant. HS: Highly Signficant.

and FokI) and dental caries in Iraqi children. Individuals with the CC genotype of VDR polymorphisms FokI have a 2.7-fold increased likelihood of developing active caries (odd ratio = 2.745, with a 95% confidence interval = 1.077 - 6.996, P-value = 0.026).

We found a definite correlation between active caries and the Fok1 in VDR CC genotypes. This discovery may be used to determine how hereditary immunological deficiencies, inflammatory alterations, and host vulnerability affect a person's risk of developing caries. Due to the existence of FokI polymorphic gene at the gene's start site (start codon) may result in the production of vitamin D proteins of various sizes that could significantly affect the caries vulnerability in study samples.

Yu et al. did comparable research in the Chinese population that confirmed our results, and this SNP was shown to have a substantial connection with dental caries in permanent dentition. The incidence of the TT genotype and T allele was considerably lower in the patient group compared to the caries-free control group, whereas the CT and CC genotypes were more prevalent in the patient group [23].

The meta-analysis investigated the correlation between several single nucleotide polymorphisms (SNPs) in the VDR gene and dental caries. Among all the SNPs analyzed, only the Fok1 SNP exhibited a statistically significant link with dental caries. Possible explanations for this result include the location of the Fok1 SNP and its interaction with co-transcription variables [20]. Das et al. carried out a study with the intention of determining the frequency of the Fok1 and Taq1 polymorphisms in restriction fragment length (RFLPs) in the vitamin D receptor (VDR) gene among a group of healthy people living in India, as well as examining any potential associations between these genetic

variations and levels of 25-hydroxyvitamin D. A substantial correlation was seen between the Taq1 restriction fragment length polymorphism (RFLP) and levels of 25-hydroxy vitamin D. However, no such correlation was found with the Fok1 RFLP [24]. In different research that was carried out on adults, it was discovered by Nireeksha et al. that the T allele of rs-2228570 was substantially related with the active caries condition [25]. Barbosa and colleagues carried out a study on permanent dentition of Brazilian children (8 to 11 years old) in order to look into the connection between Fok1 RFLPs in VDR and dental caries. The results of the study suggested that there was no correlation between the two variables that could be considered statistically significant suggesting the limitation of their study is the fact that dental caries was evaluated only with clinical examination and some interproximal caries might not be detected without radiographic examination also different clinical scale was used to detect dental caries [14].

In contrast, our study revealed a substantial association between individuals carrying the VDR polymorphism ApaI T allele with a caries-free status. However, no significant associations were seen between tooth decay and the TaqI and BsmI polymorphisms. The findings of this study are consistent with other research conducted by Qin et al, Izakovicova Holla et al and Kong et al, all of them reported no significant correlation between the TaqI VDR polymorphism and the likelihood of developing dental caries [10,26,27].

Contrarily, our research outcomes did not align with the study conducted by Hu et al., since their findings demonstrated a substantial relation between TaqI VDR polymorphism and the vulnerability to dental caries among Chinese individuals [28]. Additionaly; the study carried out by Cogulu et al. (2016) revealed that the TaqI genotypes present in the VDR gene have the potential to serve as a diagnostic indicator for assessing the predisposition of Turkish children to dental caries [29].

Hardy-Weinberg equilibrium (HWE) was used to calculate the expected common homozygotes, expected heterozygotes, expected rare homozygotes and states that the genotype and alleles frequencies in a population will remain constant from generation to generation in the absence of other evolutionary influences; thus, the deviation from HWE equilibrium means that something is occurring possibly evolution [30].

The discrepancy between our results and those of other case control studies may be attributable to the distinction between primary and permanent dentitions, as well as the different methodological approaches utilized, the geographical and ethnic differences and the small sample size. More well-conducted studies with larger sample sizes are needed to investigate other factors that may influence the current suggested model, as well as the association between VDR gene polymorphisms and the risk of dental caries in both children and adult patients with high caries risk.

CONCLUSION

This study designated that FokI (rs2228570) gene polymorphism was related with increased risk to dental caries. This conclusion highlights the importance of genetic polymorphisms which give the opportunity to clinicians to provide patients with a through perception of their proneness to dental caries in order to advocate effectual oral hygiene measures for controlling dental caries. This study spotlight on the fact that; in spite of the various causes of dental decay; subject susceptivity to caries is an crucial concern.

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Author's Contributions

GAAW, MJA: Conceptualization. HKAH, GAAW, MJA: Methodology. GAAW: Formal Analysis. GAAW, ZAAN: Data Curation. HKAH: Software. HKAH:Validation. HKAH: Investigation. HKAH: Resources. GAAW: Writing – Original Draft Preparation. HKAH, MJA, ZAAN: Writing – Review & Editing. HKAH, MJA: Visualization. GAAW, MJA: Supervision. GAAW: Project Administration Authorship.

Conflict of Interest

The authors declare that they have no conflicts of interest related to this study.

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Regulatory Statement

This study protocol was reviewed and approved by MUCOD (College of Dentistry Research Ethics Committee). It meets the requirements of the current Human Research Guidelines and full ethical approval has been granted under the reference number REC131.

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