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ORIGINAL ARTICLE

Low risk and High risk HPV Genotypes in Skin Tags

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ABSTRACT

Background: *Skin tags are flesh-coloured, pedunculated growths with a smooth surface, reported to have an incidence of 46% of the general population. The etiology of skin tags is still unknown, human papillomavirus skin infection is one of the associated factor. Human papillomavirus (HPV) is a small DNA virus of papovavirus family that classified into low risk HPV(6& 11) and high risk HPV (16&18) that induce malignant transformation. presence of HPV in the tissues depends on the identification of viral nucleic acids by PCR than serological methods that can't distinguish between present and past infection of HPV.* ***Objectives****: To detect the relationship between human papillomavirus skin infection and skin tags and to asses the relation between low risk and high risk HPV genotypes and skin tags clinical criteria and associated clinical conditions.* ***Methodology:*** *This study was conducted on 40 patients (20 females and 20 males) having skin tags (group I) and 20 sex and age matched subjects free from skin tags (group II). Skin biopsy was taken from each subject and Multiplex Polymerase chain reaction (PCR) was used to detect HPV types 6, 11, 16 and 18 DNA.* ***Results:*** *Family history was statistically significant higher in group I than group II (P=0.002). STs distributions were higher in neck (21, 52.5%) then axilla (11, 27.5%), back (4, 10%), abdomen (2, 5%) and the thigh(2, 5%). A significant difference in HPV positivity between the studied groups, that showed stepwise down regulation from lesional (19, 47.5%) passing by perilesional (5, 12.5%) and ended by normal skin (2, 10%) specimens (P<0.001). Moreover HPV genotype 6 was the most observed type.* ***Conclusion:*** *Human papillomavirus has a role in the pathogenesis of skin tags. Therefore using of antiviral or immunotherapy may help in skin tags management program. There is no relation between HPV genotypes and skin tags clinical criteria (sites & severity) nor associated clinical conditions.*

INTRODUCTION

Skin tags (STs), or acrochordons are common, small, soft, usually pedunculated benign skin growths[1], frequently existing in intertriginous area e.g. axilla, neck, eye lid[2]. About 46% of the general population have STs[1], both elderly and middle- aged individuals are commonly affected[3]. STs diameters vary from 2 mm to 5 mm, up to 5 cm that occasionally evident[4].

Clinically, STs presented in three types: single or many filliform protrusions, single bag like pedunculated lesions or small numerous papule[5]. Histologically, skin tags are polypoid growths with overlying slightly acanthotic epidermis and a fibrous vascular kernel dermis[6].

Until now the etiology of STs is unidentified[7]. Frequent irritation of the skin[8], metabolic syndrome, hormonal imbalance and obesity, are related factors[9] as well as human papillomavirus skin infection[10].

Human papillomavirus (HPV) is a small DNA virus of papovavirus family. More than 200 different types of HPV have been defined[11]. HPVs are classified into low risk HPVsubtypes e.g. 6 & 11 that are never found in invasive squamous carcinoma and high risk HPV subtypes such as 16 & 18 that induce malignant transformation[12]. The existence of HPV in the tissues depends on the detection of viral nucleic acids by polymerase chain reaction than serological methods that can't differentiate between present and past HPV infections[13].

In our study we aimed to investigate the relationship between human papillomavirus skin infection and skin tags and to assess the relation between low risk (6&11) and high risk (16&18) genotypes of HPV and skin tags clinical criteria with different associated clinical conditions.

METHODOLOGY

This case-control study was conducted on patients (n=40) having variable numbers of skin tags lesions. They were compared with age and sex-matched healthy volunteers (n=20) as a control group. Patients were recruited from the Outpatient Clinic of Dermatology,

Andrology and STDs Department, Menoufia University Hospital during the period from November 2017 to December 2018. A written informed consent form was signed by each participant included in this study after informing them about the study. The study was approved by the Ethical Committee of Human Right of Research (HRR) at Menoufia University.

In our study, all patients included were above the age of fifteen years with any subject having verrucae anywhere in the body was excluded.

All participants were subjected to medical history and thorough clinical examination: include evaluation of body weight and height to asses BMI[14]. Full dermatological examination was done including determination of site, number and distribution of skin tags. Severity of skin tags was assessed according to its number into mild (1-10), moderate (10-30) and severe (≥30)[15].

Laboratory investigations including: lipid profile and serum blood glucose level were performed.

A total of 100 biopsies were collected. From each patient, excisional biopsy of one skin tag (40 lesional biopsies) and 4ml punsh biopsy of non lesional skin, 5cm away from the excised skin tag (40 perilesional biopsies) were done. From the control group, site matched 20 punsh biopsies were obtained. All specimens were obtained under aseptic condition and local anesthesia by injection of mepivacaine hydrochloride. Then the specimens were collected in sterile container with saline and refrigerated at [-20 to -80°C] till time of analysis. Multiplex Polymerase Chain Reaction (PCR) was performed to detect presence of human papilloma virus (HPV) and its low (6&11) and high (16&18) risk subtypes.

Multiplex Polymerase chain reaction (PCR):

The DNA extraction kit used was supplied by QIAamp DNA Kits (Qiagen, Germany) and the manufacturer's recommendations were followed where The sample (10 gm) placed up in liquid nitrogen, mechanically disrupted and decanted into1.5 ml microcentrifuge tube. The liquid nitrogen allowed to be evaporated. Then the samples resuspended in 180 µl of Buffer ATL (digestion solution). 20 µl proteinase K solution was added and mixed by vortexing, and incubated in a shaking water bath at 56°C until the sample was completely lysed. 4µl RNaseA solution was added, mixed by pulse-vortexing for 15 s, then incubated for 2min at room temperature (15–25°C). 200 µl Buffer AL was added to the samples that were Mixed again by pulse-vortexing for 15 s, and incubated at 70°C for 10 min. 200µl ethanol (96- 100%) was added to the sample, and mixed by pulse-vortexing for 15 s. The microcentrifuge tubes were centrifuged to remove drops from inside the lid between each step. The prepared lysate was transferred to the QIAamp Mini spin column (in a 2 ml collection tube) and centrifuged at (8000 rpm) for 1 min before and after adding 500µl Buffer AW1. The QIAamp Mini spin column was placed in a clean 2 ml collection tube. The collection tube containing the filtrate was discarded. 500µl Buffer AW2 was added and centrifugation at full speed (14,000 rpm) for 3 min was done. The QIAamp Mini spin column was placed in a new 2 ml collection tube and the old collection tube was discarded with the filtrate. Centrifugation at full speed for 1 min was done. The QIAamp Mini spin column was placed in a clean 1.5 ml microcentrifugetube, and the collection tube containing the filtrate was discarded. The QIAamp Mini spin column was carefully opened and 200µl Buffer AE or distilled water was added. Incubation at room temperature for 1 min was done, and centrifugation at (8000 rpm) for 1 min was done. This step was repeated. The purified DNA was used immediately or stored – 20°C.

Primers Design:

DNA sequence files for HPV types 6,11,16,18 were obtained from Genbank (http://www.ncbi.nih.gov/genbank/) (Qiagen, Germany)[16] (Table 1).

Table 1: Sequence of primers used and their size

HPV genes	Primer sequence	Amplicon size (bp)
HPVgene 6 F **HPVgene 6** R	Acgtggccttgtgcggta cag tc Aga gac gag tcaggcaatgc	757bp
HPVgene 11 F **HPVgene 11** R	Agttccgta gat gccaagggc a Tgcctcaggtgaggcccaatg c	528 bp
HPVgene 16 F **HPVgene 16** R	Ttaggcagc act tggccaacc a Taatccgtcctttgtgtgagc t	207 bp
HPVgene 18 F **HPVgene 18**R	Tccgtggtgtgcatcccagca g Cacttgtgcatcattgtggac c	274bp
***β*-globin F** ***β*-globin R**	Gaa gag ccaaggacaggt ac Caactt cat ccacgttca cc	268bp

PCR program:

Was performed in a thermal cycler (Biometra-Germany) with the following conditions: initial denaturing step at 95°C for 15 min, 10 cycles of 30 s at 94°C, 90 s at 65°C, and 90 s at 72°C, followed by 30 cycles of 30 s at 94°C, 90 s at 63°C, and 90 s at 72°C, with a final extension at 72°C for 10 min. The amplified DNA products were detected on 1.5% agarose gels by ethidium bromide staining (Sigma, USA) and photographed under a UV transilluminator by using a Digital Kodak Science 120 system. A DNA ladder (100-1000bp) (Fermentas, Germany) was used to estimate allele sizes in base pairs (bp) for the gel. a positive control represented by β-globin gene and a negative control without a DNA template were included[16].

RESULTS

This case-control study was conducted on 40 patients with skin tags selected from Dermatology outpatient clinic, Menoufia University during the period between September 2017 and February 2019. The patients ages ranged from 19 to 65years with 41.73±11.91 as a mean±SD and 40.5 as a median value. They were 20 males (50%) and 20 females (50%), with 1:1 as male to female ratio. The BMI ranged from 22.1 –43.7 kg/m2with 30.19±5.12 as a mean ±SD and 30.85 as a median value. Out of 40 patients 25(62.5%) cases had STs positive family history.

The control group included 20 healthy individuals. Their age ranged between 21 to 61 years, with 40.75±10.77as a mean ±SD and 41.5as a median value. They were 10(50%) males and 10(50%) females. The BMI ranged from 22.8- 31.3kg/m2 with28.63±2.40 as a mean ±SD and 29.25 as a median value. Four (20%) of them had STs positive family history. There was no statistical significant difference between the studied groups regarding their age (P=0.759), gender (P=1.000) and BMI (P=0.114). Regarding STs family history there was a statistically significant increase in patients than control group (P=0.002)

The site of skin tags was neck (21, 52.5%), axilla (11, 27.5%), back (4, 10%), abdomen (2, 5%) and the thigh (2, 5%) (Fig. 1).

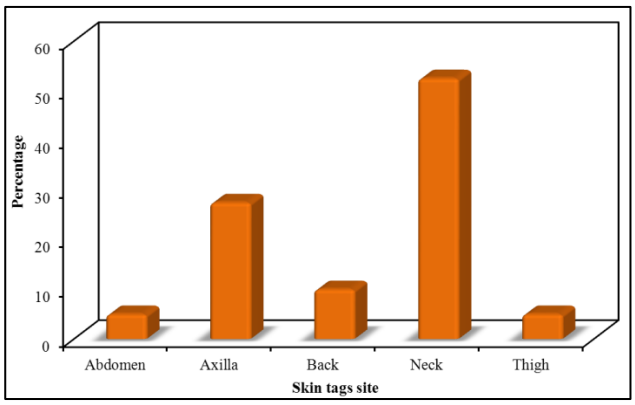

Fig.1: The site of skin tags

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Regarding the number, it ranged from 3 to 34 with 14.20 ± 8.18 as a mean ±SD and 12.50 as a median value. Severity of STs varies from mild (1-10), moderate (11-30) and severe (>30), with (3, 7.5%), (23, 57.5%) (14, 35%) of the patients had severe, moderate and mild STs respectively.

According to the associated diseases of skin tag patients, 10(25%) patients were diabetic, 6(15%) suffered from dyslipidemia, 7(17.5%) had acanthosis nigricans and 21(52.5%) cases were obese.

Regarding multiplex PCR results (Fig. 2). HPV positivity showed a significant stepwise up regulation from normal control skin (2, 10%) passing by perilesional (5, 12.5%) and ended by lesional (19, 47.5%) specimens (P <0.001). Additionally, the lesional STs specimens demonstrated a significant high HPV positivity than perilesional and normal ones (P=0.001 and P=0.004) respectively. However, the difference between perilesional and control specimens could not reach level of significance (Fig. 2 & 3).

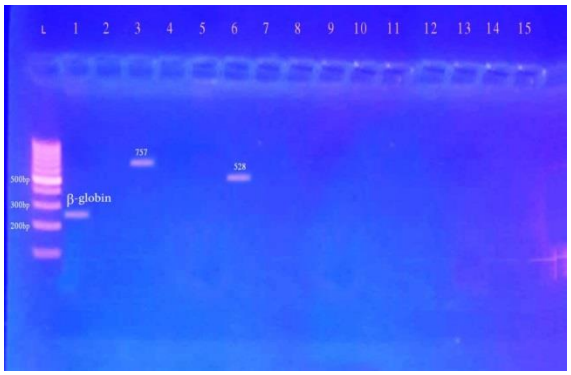

Fig. 2: Gel electrophoresis PCR of HPV type 6, 11, 16, 18 and β-globin.

Lane L: 100-1000 DNA ladder size marker. Lane 3 show the 757 bp band specific for HPV 6, lane 6 shows the 528 bp band specific for HPV 11 and lane 1 shows the 268 bp band specific for β-globin with negative results for 16 and 18 genotypes.

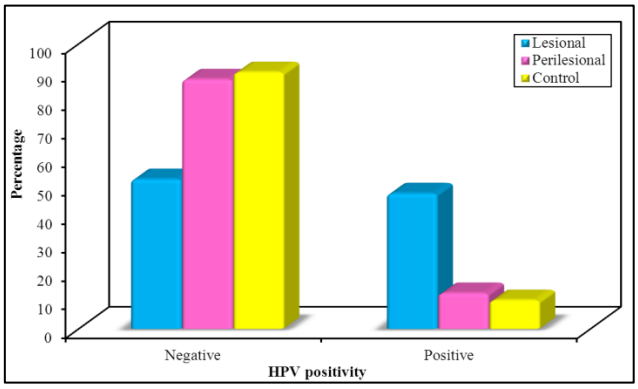

Fig. 3: Comparison between the different studied groups according to HPV positivity.

HPV genotype 6 was the most observed type that showed a significant regulation in lesional (11, 27.5%) skin biopsies (P=0.036) (Table 2).

Table 2: Comparison between the different studied groups in relation to HPV genotypes

HPV	Lesional (n = 40)		Perilesional (n = 40)		Control (n = 20)		p	Sig.bet. grps
	No.	%	No.	%	No.	%		
HPVgene types								
-HPV 6	11	27.5	3	7.5	2	10.0	0.036*	-
-HPV 11	5	12.5	2	5.0	0	0.0	^{MC}p=0.206	-
-HPV 6 ,11	3	7.5	0	0.0	0	0.0	^{MC}p=0.219	-
-HPV 16	0	0.0	0	0.0	0	0.0	–	-
-HPV 18	0	0.0	0	0.0	0	0.0	–	-

-FE: Fisher Exact
-MC: Monte Carlo-**FE:** Fisher Exact
-p: p value for comparing between **Lesional**, **Perilesional and Control**
-*: Statistically significant at $p \leq 0.05$

Studying the relation between lesional HPV positivity with demographic, associated diseases of skin tags patients and skin tags clinical criteria revealed non significant associations (P>0.05 for all) (Table 3).

Table 3: Relation between lesional HPV with demographic characters, STs criteria and associated diseases of cases (n = 40).

Variables	HPV				χ^2	p
	Negative (n = 21)		Positive (n = 19)			
	No.	%	No.	%		
Sex						
-Male	12	57.1	8	42.1	0.902	0.342
-Female	9	42.9	11	57.9		
Age (years)						
-15 –<30	5	23.8	1	5.3	2.617	^{MC}p= 0.328
-30 – 50	11	52.4	13	68.4		
-Over 50	5	23.8	5	26.3		
Family History						
-No	10	47.6	5	26.3	1.931	0.165
-Yes	11	52.4	14	73.7		
Site						
-Neck	11	52.4	10	52.6	2.091	0.866
-Axilla	5	23.8	6	31.6		
-Back	2	9.5	2	10.5		
-Abdomen	1	4.8	1	5.3		
-Thigh	2	9.5	0	0.0		
Skin tags severity						
-Mild (1 – 10)	8	38.1	6	31.6	0.673	^{MC}p= 0.893
-Moderate (10 – 30)	12	57.1	11	57.9		
	1	4.8	2	10.5		
DM						
-Normal	15	71.4	15	78.9	0.301	^{FE}p= 0.721
-High	6	28.6	4	21.1		
Dyslipidemia						
-Normal	18	85.7	16	84.2	0.018	^{FE}p= 1.000
-High	3	14.3	3	15.8		
A.N						
-Negative	18	85.7	15	78.9	0.316	^{FE}p= 0.689
-Positive	3	14.3	4	21.1		
Obesity						
-Normal weight	3	14.3	4	21.1	1.568	0.210
-Over weight	5	23	7	36.8		
-Obese	13	61.9	8	42.1		

-χ^2: **Chi square test** -FE**: Fisher Exact** -A.N: Acanthosis nigrican
-p: p value for comparing between **Negative** and **Positive**

Studying the relation between lesional HPV genotypes with demographic, associated diseases of skin tags patients and skin tags clinical criteria revealed non significant associations (P>0.05 for all).

Table 4: Relation between lesional HPV genotypes with demographic character, STs clinical criteria and associated diseases of group I (n =40).

Variables	Positive (n = 19)						χ^2	^{MC}p
	HPV 6 (n = 11)		HPV 11 (n = 5)		HPV 6, 11 (n = 3)			
	No.	%	No.	%	No.	%		
Age (years)								
-15 –<30	0	0.0	1	20.0	0	0.0		
-30 – 50	10	90.9	2	40.0	1	33.3	8.736	0.120
-Over 50	1	9.1	2	40.0	2	66.7		
Sex								
-Male	5	45.5	2	40.0	1	33.3	1.227	0.788
-Female	6	54.5	3	60.0	2	66.7		
Family History								
-No	3	27.3	2	40.0	0	0.0	2.849	0.455
-Yes	8	72.7	3	60.0	3	100.0		
Site								
-Neck	5	45.5	3	60.0	2	66.7	2.091	0.866
-Axilla	4	36.4	1	20.0	1	33.3		
-Back	1	9.1	1	20.0	0	0.0		
-Abdomen	1	9.1	0	00.0	0	0.0		
-Thigh	0	0.0	0	0.0	0	0.0		
Skin tags severity								
-Mild (1 – 10)	4	36.4	1	20.0	1	33.3	0.673	0.893
-Moderate(10 – 30)	6	54.5	3	60.0	2	66.7		
-Severe (>30)	1	9.1	1	20.0	0	0.0		
DM								
- Normal	9	81.8	4	80.0	2	66.7	0.929	0.941
- High	2	18.2	1	20.0	1	33.3		
Dyslipidemia								
- Normal	10	90.9	4	80.0	2	66.7	1.927	0.681
- High	1	9.1	1	20.0	1	33.3		
A.N								
- Negative	9	81.8	4	80	2	66.7	1.496	0.797
- positive	2	18.2	1	20	1	33.3		
Obesity								
- Normal weight (18.5 – 24.9)	3	27.2	1	20.0	0	0.0	2.545	0.525
- Over weight (25 – 29.9)	4	36.4	1	20.0	2	66.7		
- Obese (30 or more)	4	36.4	3	60.0	1	33.3		

DISCUSSION

STs are closely similar to that of mucocutaneous papillomatosis and their clinical behaviour may be reminiscent of that of laryngeal papillomas, with respect to the fact that they spread locally in the same subject, which might raise the suggestion of a common aetiology. Since HPV has been identified in many papillomas, they may consequently be responsible for the development of skin tags[17].

Therefore, this study was designed to shed light on the relation between different HPV genotypes and skin tags clinical criteria and associated clinical diseases,

through evaluation of HPV types 6, 11, 16 and 18 in skin tags by using polymerase chain reaction (PCR).

In the present study, Polymerase Chain Reaction as a sensitive and specific method for detection of viral DNA in tissues was used to search for HPV DNA 6, 11, 16 and 18 genotypes in skin tags lesions. A positive control represented by β-globin gene to ensure the quality of DNA sample and the absence of PCR inhibitors[16].

Out of the current 20 investigated control samples, 2(10%) ones demonstrated HPV positivity. Supporting the finding of *Foulongne et al.*[18], reported that cutaneous HPV is a part of the microbiological flora of the healthy human skin. A symptomatic carriage of HPV on the skin was described and may reflect viral shedding from cutaneous reservoir that may be the hair follicle. Moreover, in a study done by *Astori et al.*[19], they were able to detect HPV DNA in 35% of normal skin samples suggesting that HPV DNA may be widely distributed in normal skin of immune-competent individuals in whom intact immune system inhibits the development of disease.

In the current work, there was a significant difference in HPV positivity between the studied groups, that showed stepwise up regulation from normal skin (10%) specimens passing by perilesional (12.5%) and ended bylesional (47.5%) tissues. Therefore, we confirmed the possible role of HPV in the pathogenesis of skin tags

The result of this study was in accordance with a study done by *Gupta et al.* [20], who previously reported the presence of HPV DNA in 48.6% of biopsies taken from 37 Indian patients. Also, our results were coincided with that of Karayana *et al.*[21] who studied 16 Indonesian patients. The authors reported 14(46.7%) positive samples out of the total 30 skin tag lesions. However, *Dianzani et al.*[22] reported the presence of HPV in 88% of skin tag samples that were obtained from 49 Caucasian patients.This higher prevalence was also reported by *Sallam et al.* (76.6%) [17] and *Askar et al.*(71.4%) [10]. The presence of HPV DNA in skin tags, suggesting the possible role of these viruses in their development. On the other hand, the lack of viral transcripts could indicate a latent infection by HPV.

On the contrary, *Pezeshkpoor et al.*[23] reported that all skin tag biopsies obtained from 50 Iranian patients were negative for low risk / high risk HPV DNA. They explained the negative results of HPV PCR could be due to the lack of any link between HPV and skin tag or presence of technical error. Additionally, this discrepancy can be explained by the sensitivity of the detection technique or loss of HPV genome as HPV could have been damaged during processing of the samples. Moreover, the geographical conditions has a role in this variation as a high number of HPV infection exists in tropical parts of world, in which ultra violet light suppress dermal immunity with reducing activity of TH1 cells [20].

Skin tags are known to develop in areas of skin friction, leading to disruption of skin, which might serve as a route of entry for the virus. The existence of HPV DNA and mechanical friction seem to be significant cofactors in the skin tags pathogenesis[5].

The possible role of HPV in skin tags development has been postulated that HPV infection begins with the inoculation of the virus into the interrupted epithelium and the interaction with a putative specific cellular receptor[20]. HPV infection involves squamous epithelium and can cause growth stimulation, cell proliferation and the formation of pathologic cells[24] through the role of E5 oncoprotein, which can activate growth factor receptors causing epithelial hyperplasia and papillomatosis[21].

Regarding HPV genotypes that have a role in the pathogenesis of skin tags, the current study showed that HPV DNA type 6, 11 were significantly higher in skin tags patients than the other genotypes included in this study. HPV genotype 6 was the most observed type that showed a statistical significant in lesional skin biopsies. HPV genotype 11 was found in lesional samples (5, 12.5%) and perilesional samples (2, 5%). Parallel to our finding, many investigators[10, 17, 20, 21, 22] found that HPV genotype 6, 11presented in all HPV positive STs samples. Moreover, in accordance with previous study[10] we did not detect HPV high risk types 16 and18 in any sample. So STs are benign lesions due to absence of the high risk types of HPV which known to be responsible for malignant transformation. Against our finding, *Dianzani et al.*[25] detected HPV(16 and 18) in 50% out of ten positive samples from total 20 samples, the authors hypothesized that skin tags may represent a reservoir of carcinogenic HPVs.

As previously reported [21], we observed that there was no significant relation between HPV positivity or genotypes and the site of the skin tag. Also, in agreement with *Gupta et al.* **20.** we concluded that HPV positivity is independent of patient's gender that indicated by absence of the relationship between gender of skin tags patients and the presence of HPV infection in the current study.

As regard skin tags number, in agreement with *Sallam et al.*[17] we observed no relation between skin tags number and HPV positivity or genotypes.

Regarding the associated diseases of skin tags patients in this study (diabetes mellitus, dyslipidemia, acanthosisnigricans and obesity), in agreement with *Askar et al.*[10], there was no significant association between them and HPV positivity or its genotypes in current work.

Limitations:

Small sample size was the only limits of this study.

CONCLUSION

In this study the presence of HPV in the skin tag lesions from different sites could be a contributing factor in the development of skin tags, supporting its role in the pathogenesis of these cutaneous lesions.The identification of HPV 6/11 in these lesions, which are benign proliferations of the skin, further expands the spectrum of HPV-linked lesions. Moreover, this association may have a practical therapeutic importance through using of antiviral or immunotherapy in skin tags management. Also there there is no relation between HPV genotypes and STs clinical criteria nor associated clinical conditions.

Conflicts of interest: The authors declare that they have no financial or non financial conflicts of interest related to the work done in the manuscript.

- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

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