

# Association between Serum Zinc Levels and Multiple Cutaneous Warts: A Cross-Sectional Study

Divya Mani, Jude Ernest Dileep, Damayandhi Kaliyaperumal, Sheela Kuruvila, Jagadeeshkumar Govardhan<sup>1</sup>, Ilakkiapriya Sadasivam, Rajkiran Takharya<sup>2</sup>

Department of DVL, Aarupadai Veedu Medical College and Hospital, Puducherry, <sup>1</sup>Department of DVL, Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry, India, <sup>2</sup>Department of DVL, Manipal Tata Medical College, Jamshedpur, Jharkhand, India

## Abstract

**Background:** Warts are cutaneous manifestations of human papillomavirus (HPV). Trauma and maceration facilitate initial epidermal inoculation. The spread may then occur by autoinoculation. Local and systemic immune factors appear to influence the spread. Zinc is an essential micronutrient having a wide spectrum of actions. Deficiency of the same adversely affects the immune function, especially, T cell functions. The role of zinc as an immunological modulator activates lymphocytes and cytokines against the penetration and replication of viruses, which has increasingly been recognized. Numerous skin disorders have been linked to zinc deficiency. A high dose of oral zinc sulfate has shown outstanding therapeutic efficacy and prevents relapse in patients with recalcitrant and multiple warts. Owing to the therapeutic efficacy of oral zinc in the treatment of warts, the current study was undertaken to find out the association between serum zinc level and multiple cutaneous warts among the study population. **Materials and methods:** One hundred and ten patients with cutaneous warts met the inclusion criteria and an equal number of age and sex-matched controls were enrolled. A consecutive sampling technique was used for the enrolment. Details regarding the duration, number, clinical type, size, and distribution of the warts were recorded. Serum zinc levels were estimated in both cases and controls. Data were tabulated and analyzed using the SPSS software version 20. **Results:** The reference range for normal serum zinc levels was taken as 60–180 µg/dL. Normal serum zinc levels were found in 91 (100%) of the cases and 100 (110%) of the controls; high levels were found only in 9 (10%) of the cases. Cases were found to have significantly higher mean serum zinc levels compared with the controls. ( $121.1 \pm 35.78$  µg/dL vs.  $101.8 \pm 20.48$  µg/dL,  $P = 0.0001$ ). **Conclusion:** Patients with multiple cutaneous warts were found to have higher mean serum zinc levels compared with age and sex-matched controls. There was no significant association of serum zinc levels with the duration or the number of warts.

**Keywords:** Cutaneous, warts, HPV, zinc

## INTRODUCTION

Warts are cutaneous manifestations of human papillomavirus (HPV). Common warts, plantar warts, flat or planar warts, and genital warts are some of the clinical manifestations of HPV infection.<sup>[1]</sup> There are over 100 HPV subtypes.<sup>[2]</sup> Trauma and maceration facilitate the initial epidermal inoculation. The spread may then occur by autoinoculation.<sup>[3]</sup> Local and systemic immune factors appear to influence the spread; the immunosuppressed patients are at particular risk of developing generalized lesions that are difficult to

treat.<sup>[4]</sup> Humoral immunity provides resistance to HPV infection; the cellular immunity helps the established infection to regress.<sup>[5]</sup>

A variety of therapeutic interventions are available. The common approaches include chemical or physical destruction of the affected tissue, enhancement of the local immune response, and antiproliferative therapy.<sup>[6,7]</sup>

**Address for correspondence:** Dr. Damayandhi Kaliyaperumal, Department of DVL, Aarupadai Veedu Medical College and Hospital, Pondy Cuddalore Main Road, Kirumampakkam, Bahour Commune Panchayat, Puducherry 607402, India. E-mail: deepakaliyaperumal@gmail.com

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Zinc is an essential micronutrient having a wide spectrum of actions. The zinc deficiency adversely affects the immune function, especially, T cell functions.<sup>[8]</sup> Zinc as an immunological modulator, activates lymphocytes, releasing cytokines against the penetration, and replication of the viruses.<sup>[9]</sup> A high dose of oral zinc sulfate has shown outstanding therapeutic efficacy and prevents relapse in patients with recalcitrant multiple warts.<sup>[10]</sup> Owing to the therapeutic efficacy of oral zinc in the treatment of warts, the current study was undertaken to find out the association between the serum zinc level and multiple cutaneous warts among the study population.

## MATERIALS AND METHODS

This comparative study was conducted in the Department of Dermatology of a tertiary care teaching hospital in South India, from December 2020 to June 2022. Patients with a clinical diagnosis of multiple cutaneous warts were included in this study. The duration of the disease, number, types of warts, size, and distribution of the warts were noted.

All patients aged 10–56 years with multiple (more than three) cutaneous viral warts attending the Dermatology Outpatient Department, without any other dermatological diseases were included in study. Patients who were not willing to participate in the study, patients who were on zinc supplementation or any immunosuppressive therapies, and those with chronic diarrhea and acrodermatitis were excluded.

One hundred and ten patients with cutaneous viral warts meeting the inclusion criteria were enrolled. The consecutive sampling technique was used. The same number of healthy individuals were taken as controls after matching with the age and sex. An informed written consent was taken from the patients. Venous blood sample from each control and study participant was taken for the zinc level assessment. The serum zinc level estimation was done by Nitro-2-(5-Nitro-2-pyridylazo)-5-(N-propyl-3-sulfopropylamino) Phenol disodium salt, dihydrate methods using Sigma–Aldrich Kit (Bangalore). The normal range of serum zinc level was considered to be 60–180 µg/dL.

The data were fed in Microsoft Excel and analyzed by the Statistical Package for Social Service (SPSS)-version 20, IBM (Chicago, IL,USA). Descriptive data were expressed in mean ± standard deviation along with the frequency table. The mean of continuous variables was compared using the two-tailed independent Student *t* test, and qualitative variables were compared using chi-square test. The correlations were computed by Pearson's correlation coefficient. *P* value of ≤0.05 was considered to be statistically significant.



Figure 1: Multiple warts over the face



Figure 2: Verruca vulgaris over the dorsum of left foot

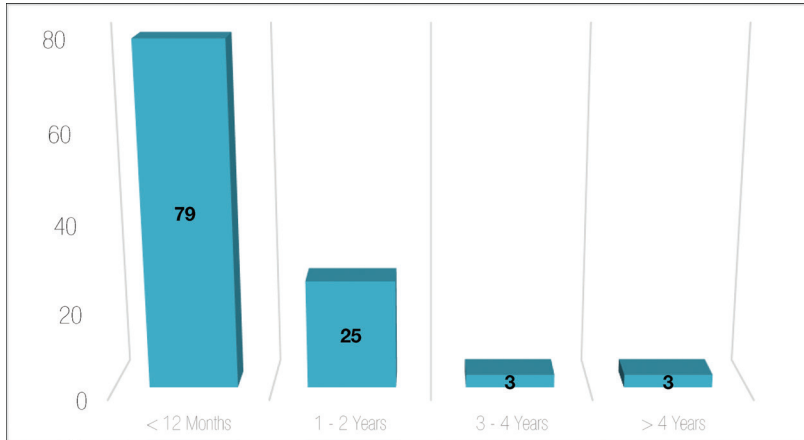
## RESULTS

The study consisted of two groups, among which 110 were cases with multiple cutaneous warts, and 110 were healthy controls. More number of participants belonged to the age group of 20–39 years in both, cases 45 (41%) and control 50 (45.5%) groups. The mean age of the cases was 31.41 years, and controls was 31.57 years. Males were 66 (60%), and females were 44 (40%) among the cases. Regarding the duration of warts, 79 (72%) cases had warts for <12 months duration, followed by 25 (22%) who had warts for 1–2 years and 6 (6%) for >3 years. Fifty (46%) cases had 4 warts followed by 39 (35%) who had 5–10 warts and 21 (19%) who had >10 warts. A more common type of wart is verruca vulgaris observed in 38 (34.5%) cases, followed by palmar wart in 20 (18%) cases and filiform warts in 15 (13%) cases [Figures 1 and 2]. More than two types of warts were observed in 37 (33.6%) cases [Table 1]. We observed that 37 (34%) of the warts were present on the right and left hand followed by 9 (8%) on the face and 6 (5%) on the neck. We also observed a few warts on the lips,

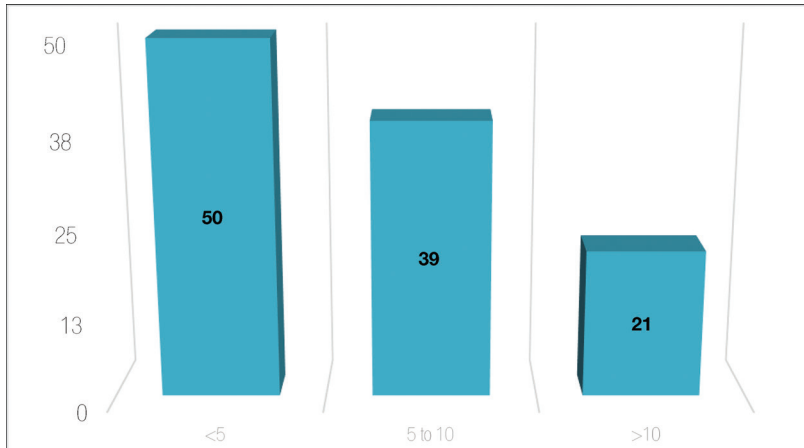


**Table 1. Continued**

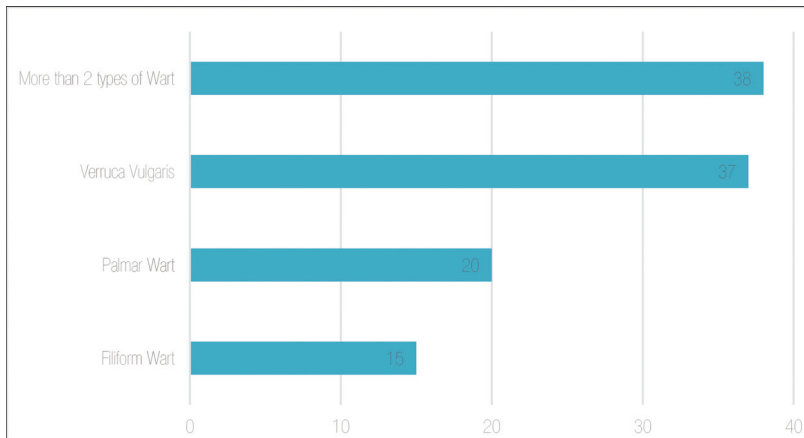
Variables	Study group	Control group	P value
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Bar diagram representing the distribution of duration of warts among study participants.



Bar diagram representing the distribution of number of warts among study participants.



Bar diagram representing the distribution of types of warts among study participants.

NA = not applicable, SD = standard deviation

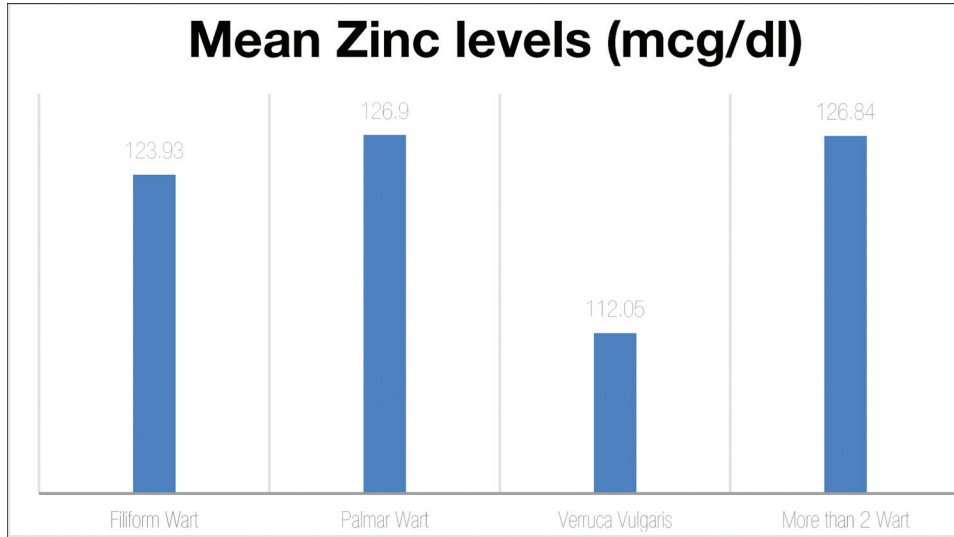
nose, eyelids, neck, scalp, and arms. Warts were present in more than two sites in 43% of the cases.

From the current study, we observed that there is no significant difference in serum zinc levels among different types of warts ( $P = 0.176$ ) and different numbers of warts

[Table 2]. In this study, the normal serum zinc reference range was taken as 60–180  $\mu\text{g/dL}$ . Normal levels were observed in 100 (91%) of the study participants and 110 (100%) in the control group; high levels were observed in 10 (9%) of the study participants in the case group [Table 3].

**Table 2: Statistical comparison of serum zinc level between different types of warts**

Type of warts	Zinc levels ( $\mu\text{g/dL}$ )	95% confidence interval for mean		Minimum	Maximum	P value
		Lower bound	Upper bound			
Filiform wart	123.93 $\pm$ 29.03	107.85	140.01	85	185	0.176 (NS)
Palmar wart	129.10 $\pm$ 40.925	109.95	148.25	73	219	
Verruca vulgaris	111.39 $\pm$ 31.59	101.01	121.78	68	265	
More than two warts	125.65 $\pm$ 38.45	112.83	138.47	81	216	
Total	121.12 $\pm$ 35.78	114.36	127.88	68	265	

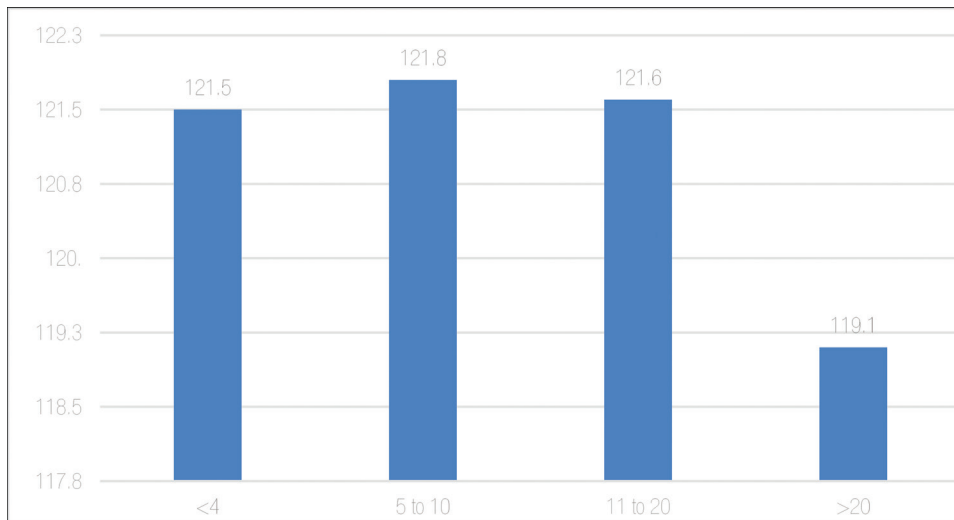


Statistical comparison of Serum Zinc Level between different types of warts.

NS, not significant

**Table 3: Statistical correlation of zinc level with different numbers of warts**

Number of warts and parameters	Minimum	Maximum	Mean	Standard deviation	P value
<4	68.00	265.0	121.5	41.53	0.9978 (NS)
5–10	81.00	216.0	121.8	31.71	
11–20	89.00	219.0	121.6	36.77	
>20	81.00	141.0	119.1	19.92	



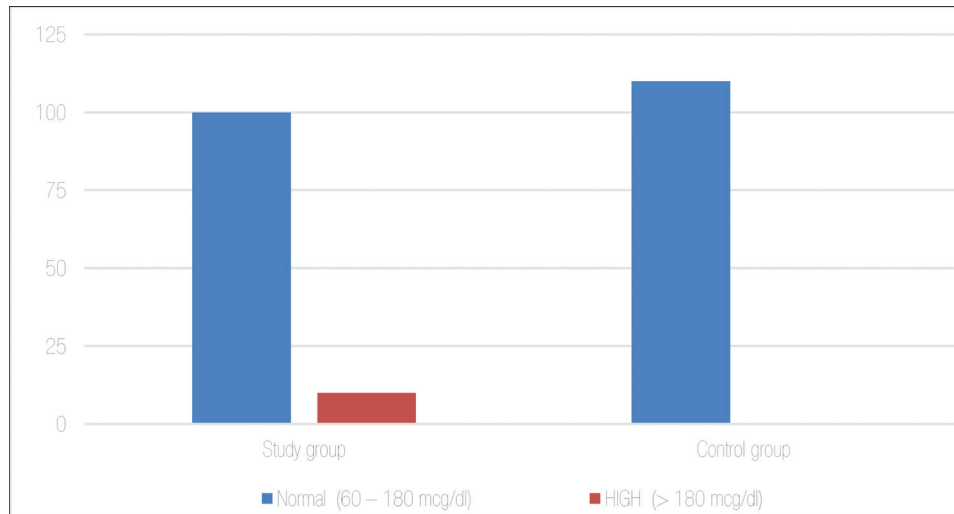
Statistical correlation of Zinc levels with different numbers of warts

NS, not significant

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**Table 4: Comparison of serum zinc level between the groups**

Serum zinc level	Study group	Control group	P value
60–180 µg/dL (normal)	100 (91%)	110 (100%)	<b>0.001</b>
>180 µg/dL (high level)	10 (9%)	0	
Mean ± SD	121.1 ± 35.78	101.8 ± 20.48	



Bar diagram representing the distribution of serum zinc levels among study and control groups

SD, standard deviation; Bold value represents  $P < 0.05$ 

The mean zinc level of the study group was  $121.1 \pm 35.78$  µg/dL, and the control group was  $101.8 \pm 20.48$  µg/dL, which was significantly higher in the study group [Table 4].

## DISCUSSION

Warts are benign lesions that occur in the mucosa and skin.<sup>[11]</sup> Warts are caused by the HPV, with over 100 types of HPV identified. HPV may occur at any site. The primary manifestations of HPV infection include common warts, genital warts, flat warts, deep palmoplantar warts (*Myrmecia*), focal epithelial hyperplasia, epidermodysplasia verruciformis, and plantar cysts. Warts may be transmitted by direct or indirect contact. Events that disrupt the normal epithelial barrier increase the likelihood of developing warts. Warts often resolve spontaneously within a few years. Some high-risk HPV subtypes are associated with malignancies. Based on their association with cervical cancer and precursor lesions, HPVs can also be grouped into high-risk and low-risk HPV types. Low-risk HPV types include types 6, 11, 42, 43, and 44. High-risk HPV types include types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70. Included in the high-risk group are some HPV types that are less frequently found in cancers but are often found in squamous intraepithelial lesions. HPV types 5, 8, 20, and 47 have oncogenic potential leading to epidermodysplasia verruciformis.

Acanthosis, digitated epidermal hyperplasia, papillomatosis, compact orthokeratosis, hypergranulosis, tortuous capillaries

inside the dermal papillae, and vertical tiers of parakeratotic cells with red blood cells entrapped above the ends of the digitations are the histopathologic characteristics.

The treatment options include chemical agents (salicylic acid, lactic acid, monochloroacetic, bichloroacetic acids, trichloroacetic acid, formalin, and glutaraldehyde), antimetabolic agents (5-fluorouracil, bleomycin, and podophyllin resin podophyllotoxin), cryotherapy, surgery, immunotherapies (cimetidine, interferon, diphencyprone, oral zinc supplementation, levamisole, and intralesional purified protein derivative/vitamin D3/measles, mumps, rubella/bacille calmette-guerin/trichophytin).

In our study, we observed that males (60%) were more in number compared with females (40%). Our study also reported that a greater number of participants belong to the age group of 20–39 years (41%), the mean age of the study group was 31.41 years, and the control group was 31.57 years. Sixty percent of the study group participants were male, and 40% were female. A greater number of participants belonged to the age group of 20–39 years in both study (41%) and control (45.5%) groups.

In a similar study done by Luong *et al.*<sup>[11]</sup> estimating serum zinc level in 78 patients with multiple warts, 41 were males and 37 were females, and the mean age of the study group was 32.37 years. Another similar study was done by Raza *et al.*<sup>[12]</sup> reported the age of the patients ranged from 12 to 65 years, and the mean age of the study group was  $25.88 \pm 8.90$  years, and the majority of the patients were in the age group of 21–30 years ( $n = 30, 40\%$ ). Out of

75 patients, 52 (69.3%) were males, and 23 (30.7%) were females. In a study done by Ranjit *et al.*,<sup>[13]</sup> the frequency of distribution of cutaneous viral warts was more among the males (54%) compared with females (46%), in accordance with our findings. The male predominance noted in the present study could be because of a greater likelihood of occupational trauma and environmental exposure among men.

In this study, we observed 72% of the patients were having warts for <12 months duration, 22% of the cases were having warts for 1–2 years duration, 6% of the cases were having warts for more than years, and 46% of the cases were having <5 warts followed by 5–10 warts (35%) and >10 warts (19%). A study done by Naseri *et al.*<sup>[14]</sup> observed most of the patients had  $\geq 20$  warts on the body surface, half of them were located on the upper extremities, and the duration of disease was less than 1 year in 70% of patients and more than 2 years in 16.7% of them.

In the current study, the most common type of wart we observed was verruca vulgaris in 35% followed by palmar wart in 18% and filiform wart in 13% of the participants. More than two types of warts were observed in 34% of the participants.

In our study, the normal serum zinc reference range was 60–80  $\mu\text{g/dL}$ , normal level was observed in 91% of the cases, and a high level was observed in 9% of the cases. The mean serum zinc level was  $121.43 \pm 35.78 \mu\text{g/dL}$  in cases, which was significantly higher than that of controls. No cases were seen with decreased serum zinc levels in our study. We also observed that there was no significant difference in serum zinc levels among different types of warts ( $P = 0.176$ ), also there was no significant difference in zinc level among the number of warts.

In contrast to our finding, many studies have reported decreased serum zinc levels in patients with multiple cutaneous warts. In a study done by Luong *et al.*,<sup>[11]</sup> the serum zinc level in patients with genital warts had a mean  $\pm$  SD value of  $81.83 \pm 13.99 \mu\text{g/dL}$ . Meanwhile, the mean  $\pm$  SD value of the serum zinc concentration in the control group was  $86.66 \pm 17.58 \mu\text{g/dL}$ . While the patients tend to have a lower zinc concentration in the serum compared with controls, the difference between the two groups was insignificant. Another similar study by Naseri *et al.*<sup>[14]</sup> observed the mean serum zinc concentration in the patient and control groups was  $55.2 \pm 9.6$  and  $55.8 \pm 8.2 \mu\text{g/100 mL}$ , respectively. No significant difference in serum zinc concentration was found between the two groups ( $P = 0.795$ ).

Another similar study by Raza *et al.*<sup>[12]</sup> observed serum zinc level was low in 42 (56%) patients and 24 (32%) controls ( $P = 0.003$ ). Among the patients, serum zinc level ranged from 69.5 to 109  $\mu\text{g/dL}$  with a mean of 80.4, whereas the level ranged from 69 to 110  $\mu\text{g/dL}$  with a

mean of  $83.6 + 91.04 \mu\text{g/dL}$  among controls ( $P = 0.044$ ). Ranjit *et al.*<sup>[13]</sup> observed the difference in mean serum zinc levels in cases ( $80.50 \pm 37.24 \mu\text{g/dL}$ ) and controls ( $104.31 \pm 25.31 \mu\text{g/dL}$ ) was statistically significant ( $P = 0.0001$ ). A strong association between low serum zinc level and cutaneous viral warts was seen with odds ratio of 7.37 (95% CI = 1.98–27.31;  $P = 0.0028$ ). Serum zinc level was negatively correlated with number of lesions ( $P = 0.001$ ), largest size of the lesion ( $P = 0.039$ ), and site of the lesions ( $P = 0.002$ ).

In our study, zinc deficiency was not observed among the study group with cutaneous warts, on the contrary, we observed an increased level of serum zinc in cases with cutaneous warts. Furthermore, multicentric studies with larger sample sizes are needed to further investigate the role of serum zinc in multiple cutaneous warts.

## CONCLUSION

From the study, we concluded the mean serum zinc levels in patients with multiple cutaneous warts were significantly higher than that of controls, which is contrary to many other studies. Our study also reported there was no significant association between serum zinc levels and duration or number of warts. Furthermore, a multicentric study with a larger sample size and therapeutic interventional trial could further establish the relation between serum zinc levels and cutaneous warts. This could bring potential prognostic and therapeutic applications in patients with multiple cutaneous warts, in the future.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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