

# Zinc Deficiency in Patients with Persistent Viral Warts

Naeem Raza<sup>1</sup> and Dilshad Ahmed Khan<sup>2</sup>

## ABSTRACT

**Objective:** To determine the association of low serum zinc levels with persistent, progressive or recurrent viral warts.

**Study Design:** A comparative study.

**Place and Duration of Study:** Dermatology outpatient department of Combined Military Hospital, Abbottabad in collaboration with Department of Chemical Pathology, Army Medical College, Rawalpindi, from June 2006 to May 2007.

**Methodology:** Seventy five patients having warts of more than six months duration, more than 10 in number, who either not responded to or had recurrence after previous treatments for viral warts and not having other chronic dermatological or systemic illness were included in the study after informed consent. Seventy five age and gender matched healthy individuals were taken as control. Serum zinc analysis was carried out by atomic absorption spectrometry using Perkin elmen (USA) apparatus. Independent sample t-test was used to compare mean zinc levels in microgram/litre with significance at  $p < 0.05$ .

**Results:** Age of the patients as well as controls ranged from 12-65 years with a mean of  $25.88 \pm 8.90$  years. Serum zinc level was low in 42 (56%) patients and 24 (32%) controls ( $p=0.003$ ). Among the patients, serum zinc level ranged from 695-1090 micro-gram/litre with a mean of  $804.38 \pm 100.60$ , whereas the level ranged from 690-1100 microgram/litre with a mean of  $836.17 \pm 91.04$  among controls ( $p 0.044$ ).

**Conclusion:** Zinc deficiency is associated with persistent, progressive or recurrent viral warts in the studied patients. Randomized controlled trials with careful dose adjustment of oral zinc sulphate may be helpful to formulate guide lines to manage such patients.

**Key words:** Warts. Recalcitrant viral warts. Zinc Sulphate. Papilloma. Human papilloma virus.

## INTRODUCTION

Cutaneous viral warts are benign epidermal proliferations caused by Human Papilloma viruses (HPV). Viral warts are common afflictions, affecting mostly children and young adults.<sup>1,2</sup> Humoral immunity provides sufficient protection against HPV infection. If the infection does develop, innate and adaptive cell mediated immunity is important for the eventual elimination of the infection. However, the reasons for apparent failure of the immune system in otherwise healthy individuals to clear warts for months or years remains incompletely understood. Viral warts among these individuals do not respond to conventional therapies or soon recur after destructive procedures and persist for months and years altogether till the time, the balance turns in favour of the immune system and the warts cease to exist.

Although almost all nutrients in the diet play a crucial role in maintaining an optimal immune response,<sup>3</sup> zinc is known to play a central role in the immune system, and

zinc-deficient persons experience increased susceptibility to a variety of pathogens.<sup>4-6</sup> Furthermore, the activities of many immuno-stimulants frequently used in immunologic studies are influenced by zinc concentration.<sup>7</sup> However, the immunity is delicately regulated by zinc and decreased levels result in a disturbed immune function.<sup>8</sup> The role of zinc has been observed in the treatment of certain dermatological conditions like chronic aphthous stomatitis, recurrent herpes labialis, cutaneous leishmaniasis, viral warts, etc.<sup>9-12</sup> Considering the role of zinc in immune-modulation, this study was conducted with the objective of determining the association of serum zinc levels with persistent, progressive or recurrent viral warts.

## METHODOLOGY

The study was conducted at the Dermatology outpatient department of the Combined Military Hospital, Abbottabad in collaboration with the Department of Chemical Pathology, Army Medical College, Rawalpindi over a period of one year from June 2006 to May 2007. It was approved by the Scientific and Ethics Committee of the hospital.

All patients reporting sick, on account of viral warts at the dermatology outpatient department of the hospital during the period of study were interviewed in detail and examined thoroughly. Their history included age, gender, duration of the disease, previous treatment for warts and family history of viral warts. During

<sup>1</sup> Department of Dermatology, PAF Hospital Faisal, Karachi.

<sup>2</sup> Department of Pathology, Army Medical College, NUST, Rawalpindi.

**Correspondence:** Dr. Naeem Raza, Consultant Dermatologist, PAF Hospital Faisal, Shahrah-e-Faisal, Karachi.  
E-mail: naeemraza561@hotmail.com

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dermatological examination, types, sites and number of the warts were also noted. Patients having warts of more than six months duration, more than 10 in number, those who either not responded to or recurred after previous treatments for viral warts and those having no chronic dermatological or systemic illness were included in the study. A total of seventy five patients clinically diagnosed for different types of viral warts fulfilling study criteria were included in the study after informed consent. Seventy-five age and gender matched healthy individuals were taken as control. The controls were selected from the general population and included those having no past or present history of viral warts and any chronic dermatological or systemic disease. A pre-designed proforma was filled for each patient and control separately.

Five ml of blood sample was taken from each patient as well as control after history and examination. After centrifugation, serum samples were stored in already labeled and capped glass tubes and kept frozen at -20 degrees Centigrade until analyzed for zinc. Serum zinc analysis was carried out by atomic absorption spectrometry using Perkin elmen (USA) apparatus. Serum zinc level within the range of 800-1200 microgram per litre was taken as normal. Coefficient of variation of zinc analysis was 4.3%.

Data was entered and results were analyzed statistically using SPSS 10. Frequencies and percentages were obtained for the variables where applicable. Mean and standard deviation were calculated for continuous variables. Proportions of patients and controls with low serum zinc level were compared using a chi-square test. The mean of serum zinc levels among patients was compared with that of controls using an independent sample t-test. A p-value less than 0.05 was taken as being statistically significant.

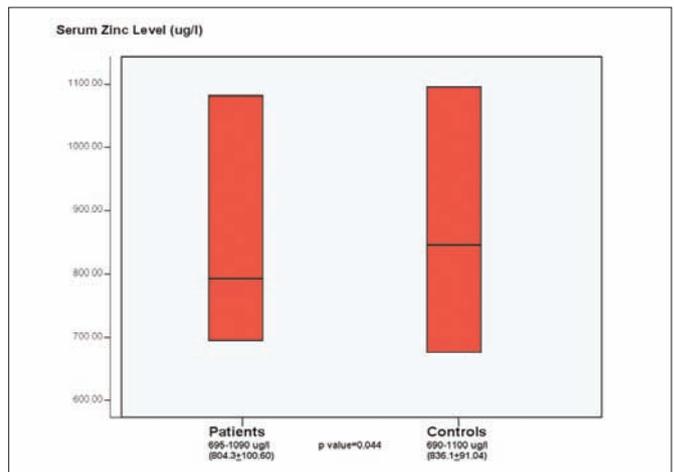
**RESULTS**

Seventy five patients and an equal number of age and gender matched healthy controls were recruited in the study. The age of the patients as well as the controls ranged from 12-65 years with a mean of 25.88 ± 8.90 years. The majority of the patients were in the age group 21-30 years (n=30, 40%) of the 75 patients, 52 (69.3%) were males and 23 (30.7%) were females. Facial warts (n=34, 45.3%) was the most common presentation followed by plane warts (n=16, 21.3%) whereas genital warts (n=02, 2.7%) were the least common. The face (n=34, 45.3%) was the most common site followed by the feet (n=20, 26.7%) whereas external genitalia and groins (n=02, 2.7%) were the least commonly involved sites. Duration of the warts ranged from 08-36 months with a mean of 16.80 ±6.88 months (Table I). A history of viral warts was present in the household of 11 (14.7%) patients.

**Table I:** Demographic profile of patients and pattern, distribution and duration of warts (n=75).

	Number	Percentage
Demographic features		
Gender		
Male	52	69.3%
Female	23	30.7%
Age (years)		
11-20	24	32.0%
21-30	30	40.0%
31-40	16	21.4%
41-50	04	05.3%
61-70	01	01.3%
Characteristics of warts		
Type of warts		
Facial warts	34	45.3%
Plane warts	16	21.3%
Mixed warts	09	12.0%
Common warts	08	10.7%
Plantar warts	06	08.0%
Genital warts	02	02.7%
Sites of warts		
Face	34	45.3%
Feet	20	26.7%
Hands	13	17.3%
Forearms	06	08.0%
Groin and external genitalia	02	02.7%
Duration (months) of warts		
> 06-12	37	49.3%
> 12-18	17	22.7%
> 18-24	15	20.0%
> 24-30	04	05.3%
> 30-36	02	02.7%

The serum zinc level was low in 42 (56%) patients and 24 (32%) controls (p=0.003). Among patients, the serum zinc level ranged from 695-1090 micro-gram/litre with a mean of 804.38 ± 100.60, whereas the level ranged from 690-1100 microgram/litre with a mean of 836.17± 91.04 microgram/litre among controls (p=0.044, Figure 1).



**Figure 1:** Serum zinc levels of patients in comparison with those of controls (n=75+75).

## DISCUSSION

Although humoral and cell mediated immune responses are sufficient against viral warts, molecular and cellular mechanisms of the immunity against the virus are not completely established.<sup>13</sup> Once the infection is established, HPV has several mechanisms to avoid the immune system. Despite viral immune evasion, the immune system effectively clears most HPV infections,<sup>14</sup> which resolve without any medical intervention. However, sometimes, the infection remains persistent, progressive or recurrent probably because of some defect in immunity against the virus.

A deficiency of zinc is said to have an adverse effect on cell mediated immunity. It appears that zinc may play a very important and critical role in the functions of human T-cells. Zinc is required for the biological activity of thymulin-a thymus specific hormone, which induces several T-cell markers and promotes T-cell functions. It has been suggested that zinc affects mainly the functions of Th<sub>1</sub> cells. Even a mild deficiency of zinc in humans may be accompanied by an imbalance of Th<sub>1</sub> and Th<sub>2</sub> cells, decreased serum thymulin activity, decreased recruitment of T naive cells, a decreased percentage of T cytolytic cells, and decreased NK cell lytic activity.<sup>15</sup> Zinc is crucial to the normal development of immune cells, and it plays an important role in maintaining the activity of a range of immune cells, including neutrophils, monocytes, macrophages, natural killer cells, and B and T cells.<sup>16,17</sup>

A nutritional deficiency of zinc is prevalent in developing countries.<sup>18</sup> It is caused by the ingestion of high cereal protein intake, rich in phytate, which makes zinc unavailable for absorption. Moreover, the main dietary source of zinc and other micronutrients i.e. animal source foods are in general less frequently available to the masses in developing countries.<sup>19,20</sup> Other common causes of zinc deficiency include malabsorption syndrome, blood loss due to hookworm infection, and excessive sweating in hot tropical climates.<sup>21</sup>

In this study, 32% healthy controls and 56% patients having viral warts had serum zinc levels below the normal range which clearly indicates that although a considerable proportion of our population is deficient in zinc, this deficiency is present in a higher number of patients with persistent, progressive or recurrent viral warts as the difference was statistically significant. The serum zinc level of patients in this study was 695-1090 micro-gram/litre with a mean of 804.38±100.60 whereas, Al-Gurairi, *et al.* reported a serum zinc level of 442.2-853.4 micro-gram/litre (mean 644.4±111.3) in patients with recalcitrant warts.<sup>12</sup> Although serum zinc levels in this study were lower, this difference may be due to different standards or techniques used or because of other nutritional deficiencies. An estimation of serum zinc levels by the photometric method is less accurate

whereas an estimation by atomic absorption, the method we employed in this study, is a fairly accurate method for estimation of metals including zinc.

Numerous studies have shown the relationship of zinc deficiency with infections and the benefits of zinc with respect to these diseases in human.<sup>6,16</sup> A study from Iraq revealed that viral warts completely disappeared in more than 60% of the patients treated with oral zinc sulphate for one month.<sup>12</sup>

Although the benefits of zinc therapy in certain infections and other diseases have been documented, the immune function is delicately regulated by zinc. Moreover, the issue of adverse effects in terms of tolerability needs to be considered. Therefore, zinc supplementation must be meticulously supervised and it may require some time to adjust the dose in an individual patient. We recommend carrying out studies for the treatment of persistent, progressive or recurrent warts with different dosages of oral zinc sulphate to find out its tolerable and effective dose for clearance of viral warts.

Zinc deficiency was found in 56% of the patients in this study; the remaining patients had serum zinc levels within normal limits. This finding probably suggests that factors other than serum zinc deficiency like other nutritional deficiencies may also be operative in immunity failure against clearance of viral warts. There was a history of viral warts among one or more members of the household of approximately 15% patients. Although it may not be easy to determine the reason keeping in view the inefficacy of warts, zinc or other deficiencies may well be a common link among the family members having viral warts. One of the limitations of this study was that these factors were not taken into account and need due consideration for further research.

## CONCLUSION

Zinc deficiency was associated with persistent, progressive or recurrent viral warts in a majority of the patients. Randomized controlled trials with careful dose adjustment of oral zinc sulphate may be helpful to manage such patients.

## REFERENCES

1. Silverberg NB. Human papillomavirus infections in children. *Curr Opin Pediatr* 2004; **16**:402-9.
2. Hutchinson DJ, Klein KC. Human papillomavirus disease and vaccines. *Am J Health Syst Pharm* 2008; **65**:2105-12.
3. Ferencik M, Ebringer L. Modulatory effects of selenium and zinc on the immune system. *Folia Microbiol (Praha)* 2003; **48**:417-26.
4. Bari AU, Mahmood T, Rahman SB, Rashid H, Iqbal Z. Zinc: an overview and therapeutic role in clinical medicine. *Pak J Pathol* 2004; **15**:28-34.
5. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. *Am J Clin Nutr* 1998; **68** (2 Suppl):447S-63S.

6. Hamer DH, Sempértégui F, Estrella B, Tucker KL, Rodríguez A, Egas J, *et al.* Micronutrient deficiencies are associated with impaired immune response and higher burden of respiratory infections in elderly ecuadorians. *J Nutr* 2009; **139**:113-9.
7. Ibs KH, Rink L. Zinc-altered immune function. *J Nutr* 2003; **133** (Suppl 1): A1452S-6S.
8. Rink L, Gabriel P. Extracellular and immunological actions of zinc. *Biometals* 2001; **14**:367-83.
9. Sharquie KE, Najim RA, Al-Hayani RK, Al-Nuaimy AA, Maroof DM. The therapeutic and prophylactic role of oral zinc sulfate in management of recurrent aphthous stomatitis (ras) in comparison with dapsone. *Saudi Med J* 2008; **29**:734-8.
10. Femiano F, Gombos F, Scully C. Recurrent herpes labialis: a pilot study of the efficacy of zinc therapy. *J Oral Patbol Med* 2005; **34**:423-5.
11. Sharquie KE, Najim RA, Farjou IB, Al-Timimi DJ. Oral zinc sulphate in the treatment of acute cutaneous leishmaniasis. *Clin Exp Dermatol* 2001; **26**:21-6.
12. Al-Gurairi FT, Al-Waiz M, Sharquie KE. Oral zinc sulphate in the treatment of recalcitrant viral warts: randomized placebo-controlled clinical trial. *Br J Dermatol* 2002; **146**:423-31.
13. Frazer IH. Interaction of human papilloma viruses with the host immune system: a well evolved relationship. *Virology* 2009; **384**: 410-4. Epub 2008 Nov 4.
14. Stanley M. Immune responses to human papilloma virus. *Vaccine* 2006; **24** (Suppl 1):S16-22.
15. Prasad AS. Zinc mechanisms of host defense. *J Nutr* 2007; **137**:1345-9.
16. Prasad AS, Beck FWJ, Bao B, Fitzgerald JT, Snell DC, Steinberg JD, *et al.* Zinc supplementation decreases incidence of infections in the elderly: effect of zinc on generation of cytokines and oxidative stress. *Am J Clin Nutr* 2007; **85**:837-44.
17. Heyland DK, Jones N, Cvijanovich NZ, Wong H. Zinc supplementation in critically ill patients: a key pharmac-nutrient? *JPENJ Parenter Enteral Nutr* 2008; **32**:509-19. Epub 2008 Jul 31. Comment in: p. 582-4.
18. Abdulla M, Suck C. Blood levels of copper, iron, zinc, and lead in adults in India and Pakistan and the effect of oral zinc supplementation for six weeks. *Biol Trace Elem Res* 1998; **61**: 323-31.
19. Allen LH. To what extent can food-based approaches improve micronutrient status? *Asia Pac J Clin Nutr* 2008; **17** (Suppl 1)103-5.
20. Bhutta ZA. Iron and zinc intake from complementary foods: some issues from Pakistan. *Pediatrics* 2000; **106**:1295-7.
21. Prasad AS. Zinc in human health: effect of zinc on immune cells. *Mol Med* 2008; **14**:353-7.

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