

ZINC DEFICIENCY AND ORAL ZINC SULPHATE TREATMENT IN PATIENTS WITH PERSISTENT VIRAL WARTSFatma H. Shabaka¹, Laila A. Rashed², Abeer M. Kamel^{1*}, Inass M. Mohammed¹ and Nohir M. Assem¹¹Department of Dermatology and Venereology, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt.²Department of Biochemistry and Molecular Biology, Faculty of Medicine, Cairo University, Egypt.

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ABSTRACT

Background: Warts are common viral infections of the skin and mucous membranes, caused by Human papillomaviruses (HPVs). Zinc has immunomodulatory effects that could counteract viral infections by having an effect on the synthesis of cytokines. **Objective:** The aim of this work was to evaluate the efficacy and safety of oral zinc sulphate in treatment of persistent viral warts. **Subjects and Methods:** This case control study included 30 patients with multiple persistent warts and 30 age and sex matched healthy persons as controls. Patients were divided according to the type of warts into three groups: 10 patients had common warts, 10 patients had plane warts and 10 had planter warts. The serum zinc level was measured before treatment, patients received oral zinc sulfate for 2 months and serum zinc level was measured after treatment. During the treatment period the patients were examined every 2 weeks for evidence of partial or complete regression of their lesions. They were photographed before treatment, one month after and 2 months immediately after treatment. **Results:** There was statistically significant decrease in serum zinc level before treatment in patients than control ($P < 0.001$). The serum zinc level in common warts has significant decrease than plane and planter ($P < 0.005$) with no difference after treatment. All these types have statistically significant increase in serum zinc level after treatment, serum zinc level before treatment ranged from 21.7 to 68.2 $\mu\text{g/dl}$ with mean 41.3 ± 12.8 and serum zinc level after treatment with oral zinc sulfate ranged from 78.9 to 172.8 $\mu\text{g/dl}$ with mean $121.4 \pm 26.9 \mu\text{g/dl}$. All our patients were responders to the zinc sulphate treatment. **Conclusion:** oral zinc sulphate seems to be a simple, effective and safe treatment of warts.

KEYWORDS: persistent warts, oral zinc sulphate.**INTRODUCTION**

Warts are benign epithelial viral infection of the skin and mucous membranes that result from infection with HPV. Human papillomaviruses (HPVs) are small DNA viruses of the papovavirus family.^[1]

Transmission of HPV requires inoculation of the virus into the cells of the basal epithelial layer, which is thought to occur in sites prone to micro injuries.^[2]

There are many therapeutic options available for the treatment of warts, no single treatment has proven to be 100% effective. Primary treatment methods are physical destruction of warts such as electrodesiccation, laser therapy and cryotherapy. However, these treatments are not suitable for patients with multiple lesions or with fear of pain and scarring.^[3] Generation of specific immunity to papillomavirus proteins appears important for clearance, as immunosuppressed individuals with impaired cell mediated immunity clear warts more

slowly, and more commonly have recurrence after treatment.^[4]

Therefore, the goal of most researches is to find a safe, effective, simple and inexpensive agent for treatment of warts.

Zinc has immunomodulatory effects. It appears that zinc may play an 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 Th1 cells. Even a mild deficiency of zinc in humans may be accompanied by an imbalance of Th1 and Th2 cells.^[5]

The immune mechanisms in the response against HPV seem to be at least partially dependent on cell-mediated immunity because lymphocytes are seen infiltrating regressing warts, sometimes in the context of a lichenoid tissue reaction. The innate immune response, namely the

recognition of viral particles by the Toll-like receptors (TLR)-3 and-9, as well as the secretion of interferon (IFN)- β and tumor necrosis factor (TNF)- α appear to be an important part of the immune response against HPV. In addition to lymphocytes, Langerhans cells and Langerhans-like dendritic cells may also play a role in the immune response against HPV.^[6]

Zinc maintains macrophage and neutrophil functions, natural killer cell activity, and complement activity. It activates natural killer cells and phagocytic function of granulocytes and stabilizes the plasma subcellular membranes especially the lysosomes. It inhibits the expression of integrins by keratinocytes and modulates the production of TNF- α and IL-6 and reduces the production of inflammatory mediators like nitric oxide.^[7]

Subjects and Methods: This case control study included 30 patients with multiple persistent warts and 30 age and sex matched healthy persons as controls. Informed written consents were obtained from all participants. The study was approved by the research ethical committee of faculty of medicine for Girls, Al-Azhar University, Cairo and fulfilled all the ethical aspects required in human research.

Patients were divided according to the type of warts into three groups: 10 patients had common warts, 10 patients had plane and 10 had planter. And they were divided according to site into; 9 patients in face, 6 patients in foot and 15 patients in hand.

Inclusion criteria include

Patient age 20 years or more.

Patient who either not responded to or had recurrence after previous conventional therapy of warts.

The patients should stop any other medication for warts for 1 month.

Exclusion criteria include

Pregnancy and lactation.

Patients using immunosuppressant drugs.

Patients with chronic systemic illness.

History: full history was taken from patients regarding age, sex, family history of the same lesion, duration of warts, any previous treatment and systemic illnesses.

Clinical examination: The patient were fully examined to determine the clinical type of the warts, their sites and distribution.

4- Laboratory test: 5 ml of blood sample was taken from each patient before treatment as well as controls. Another blood sample was taken from each patient immediately after treatment. Blood was collected in sterile test tubes and centrifuged. Serum was separated and kept at -20°C until used for analysis for zinc. Serum zinc analysis was carried out by atomic absorption spectrometry.

The patient received oral zinc sulfate in a dose of 10ml/kg daily (up to 600 mg/day) in three divided doses (in between meals to avoid gastric side effects) for two months.

During the treatment period the patients were examined every 2 weeks for evidence of partial or complete regression of their lesion. They were photographed before treatment, one month after starting the treatment and 2 months immediately after treatment.

STATISTICAL METHODS

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 21. Numerical data were summarized using means and standard deviations or medians and ranges. Categorical data were summarized as percentages. Data were explored for normality using Kolmogorov-Smirnov test and Shapiro-Wilk test. Comparisons between the 2 groups for normally distributed data were done using the Student's t-test, Mann-Whitney test was performed for non-normally distributed variables. Comparisons between 3 groups were performed using the Kruskal-Wallis test. Chi-square was used to compare between the groups with respect to categorical data. All p-values are two-sided. P-values < 0.05 were considered significant.^[8]

RESULTS

The study included 30 patients with warts and 30 controls age and sex matched Table (1).

Patients were grouped as regard type of warts into; Common warts in 10 patients (33.3%), Plane warts in 10 patients (33.3%) and planter warts in 10 patients (33.3%).

The most frequent type of warts in female was plane warts (n = 10, 100%) followed by Common warts (n = 8, 80%) then planter warts (n = 6, 60%). While in male the most frequent type was planter (n = 4, 40%) followed by common warts (n = 2, 20%) Table (2).

Patients were divided according to sites into; 9 patients in face (30.0%), 6 patients in foot (20.0%) and 15 patients in hand (50.0%).

On comparing serum zinc level before treatment, it was found that there was statistical significant decrease in serum zinc level in patients than controls (P < 0.001) (table 3) and (fig.1)

That patients with common warts had serum zinc level before treatment ranged from 21.7 to 41.3 $\mu\text{g/dl}$ with mean $29.9 \pm 6.6 \mu\text{g/dl}$ and after oral zinc sulfate treatment their serum zinc level was ranged from 78.9 to 124.6 $\mu\text{g/dl}$ with mean $104 \pm 14.6 \mu\text{g/dl}$. In patients with plane warts the serum zinc level before treatment ranged from 32.9 to 68.2 $\mu\text{g/dl}$ with mean $46.5 \pm 10.4 \mu\text{g/dl}$ and after treatment their serum zinc level was ranged from 89.3 to

172.8 µg/dl with mean 130.6 ± 26.6 µg/dl. In patients with planter warts The serum zinc level before treatment ranged from 29.2 to 64.3 µg/dl with mean 47.4 ± 12.6 µg/dl and after treatment ranged from 86.3 to 170.6 µg/dl with mean 129.2 ± 30.4 µg/dl. The total serum zinc level before treatment ranged from 21.7 to 68.2 µg/dl with mean 41.3 ± 12.8 and serum zinc level after treatment ranged from 78.9 to 172.8 µg/dl with mean 121.4 ± 26.9 µg/dl (table 4).

The patients with serum zinc level after treatment have mean 121.4 µg/dl and the control have mean 119.1 µg/dl. the comparison was not statistically significant (table 5).

On comparing the serum zinc level between types of warts before treatment; it was found that common warts have significant decrease in serum zinc level than plane and planter warts ($P < 0.005$) while comparing serum zinc level between different types of warts after treatment, there was no statistical significant difference between them. When comparing serum zinc level before and after treatment with different types of warts, all three types have statistically significant increase in zinc level after treatment ($P < 0.025$) (table 6).

All our patients were responders to the zinc sulphate treatment(fig.2).

Table (1): Sex in patients & control.

	Group		Total	P- value
	Patients	Controls		
Sex				0.091 Test: chi-square
Female	24	18	42	
	80.0%	60.0	70.0%	
Male	6	12	18	
	20.0%	40.0%	30.0%	
Total	30	30	60	
	100.0%	100.0%	100.0%	

Table (2): Patients sex and types of warts.

	Type			Total
	Common	Plane	Planter	
Sex				
Female	8	10	6	24
	80.0%	100.0%	60.0%	80.0%
Male	2	0	4	6
	20.0%	0%	40.0%	20.0%
Total	10	10	10	30
	100.0%	100.0%	100.0%	100.0%

Table (3): Comparison between serum zinc level before treatment in patients and controls.

	Group	Mean	Std. deviation	P- value
Zinc serum – before treatment	Patients	41.3	12.8	<0.001 Test: Mann-Whitney
	Controls	119.1	15.9	

Table (4): Comparison between serum Zinc level in patients before and after treatment.

	Type											
	Common			Plane			Planter			Total		
	Mean + Std.	Min.	Max.									
Zinc serum- before Treatment µg/dl	29.9 ± 6.6	21.7	41.3	46.5 ± 10.4	32.9	68.2	47.4 ± 12.6	29.2	64.3	41.3 ± 2.8	21.7	68.2
zinc serum – after Treatment µg/dl	104.4 ± 14.6	78.9	124.6	130.6 ± 26.6	89.3	172.8	129.2 ± 30.4	86.3	170.6	121.4 ± 26.9	78.9	172.8

Table (5): Comparison between serum zinc level after treatment in patients and controls.

Group		Mean	Std. Deviation	P value
Zinc serum – after treatment	Patients	121.4	26.9	0.691
	Controls	119.1	15.9	

T-test

Table (6): Relation between type of lesions and serum zinc level before and after treatment.

Serum zinc	Type						P-vale
	Common		Plane		Planter		
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	
Before	29.9	6.6	46.5	10.4	47.4	12.6	0.005 Test: Mann- Whitney
After	104.4	14.6	130.6	26.6	129.2	30.4	0.201 Test: Mann- Whitney
P- value	0.025		0.025		0.025		

Test: Wilcoxon rank sum

Test: Wilcoxon rank sum

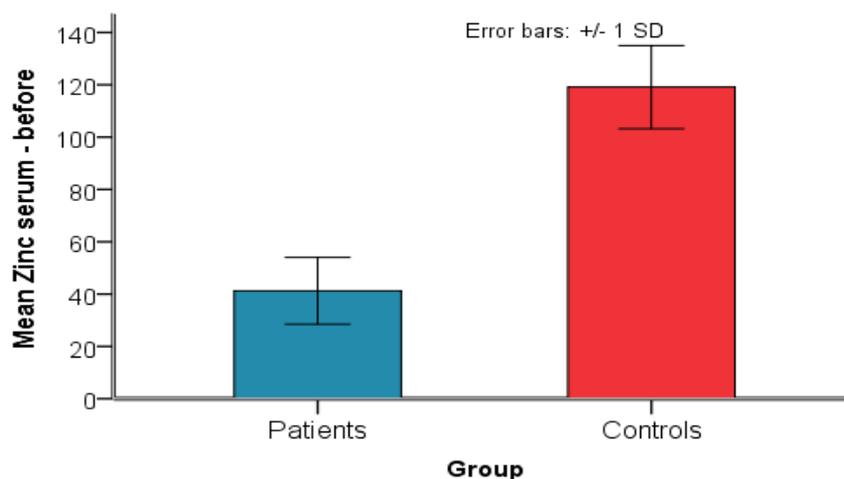


Fig.1: Comparison between serum serum zinc level before treatment in patients and controls.



Fig 2: Patient with planter warts before and after treatment.

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Table 1 Sex in patients & control.

Table 2 Patients sex and types of warts.

Table 3 Comparison between serum serum zinc level before treatment in patients and controls.

Table 4 Comparison between serum zinc level in patients before and after treatment.

Table 5 Comparison between serum zinc level after treatment in patients and controls.

Table 6 Relation between type of lesions and serum zinc level before and after treatment.

Fig.1 Comparison between serum serum zinc level before treatment in patients and controls.

Fig.2 Patient with planter warts before and after treatment.

DISCUSSION

The current study included, a total of 30 patients with multiple persistent warts completed the study (24

females and 6 males) and 30 age and sex matched healthy persons as controls. Patients were divided according to the type of warts into three groups: 10 patients had common warts(33.3%), 10 patients had plane warts(33.3%) and 10 patients had planter warts(33.3%) and according to sites into 9 patients in face (30.0%), 6 patients in foot (20.0%) and 15 patients in hand (50.0%). 80% of common warts were females and all of them were house wives. This could be explained as females are more susceptible to skin injuries, excessive water handling and pathogenic agents during their jobs. Also Grayson^[2] revealed that common warts occur in sites prone to micro injuries frequently on the hands and fingers.

There was statistically significant decrease in serum zinc level before treatment in all patients than controls. This result was supported by Al-Gurairi *et al.*^[9] who found that all their patients showed a low serum zinc level. On other hand Raza and Khan^[10] revealed that zinc deficiency was found in 56% of patients only.

The cause of zinc deficiency in our study could be due to nutritional deficiency which explained by ingestion of high cereal protein intake rich in phytate which makes zinc unavailable for absorption or may be due to blood loss due to hook worm infestation as most of our patients come from rural areas, in addition to changes in intestinal tract absorbability and permeability due in part to viral, protozoa and bacterial pathogens may also encourage fecal losses of zinc. Other common causes of zinc deficiency include exercises and excessive sweating in hot tropical climate.^[11]

In this study the mean value of zinc in patient sera was 41.3 ± 12.8 µg/dl before treatment and increase to 121.4 ± 26.9 µg /dl after treatment. The current result was supported by Sadighha^[12] who found that mean value of zinc in patients' sera was 53.3 ± 9.7 µg/dl before treatment and increase to 201.3 ± 22.0 µg/dl after treatment with oral zinc sulfate. Also there was statistically significant increase in serum zinc level after treatment in all patients with warts . Our finding revealed that patients with low serum zinc level responds to oral zinc sulphate after receiving a dose of 10mg/kg/day for two months.

Mun *et al.*^[3] and Al-Gurairi *et al.*^[9] revealed that response to treatment was directly related to the increase in serum zinc level after administration of study medications.

On comparing the serum zinc level in three types of warts, we found that the serum zinc level in common warts before treatment has significant decrease than plane and planter warts but there were no statistical significance difference between them after treatment. All these types have statistically significant increase in zinc level after treatment.

All of our patients were responders to the zinc sulphate treatment. complete clearance was achieved after two months of treatment. Thirteen cases were available for follow up with no recurrence of any lesion for 1 year.

CONCLUSION

Oral zinc sulphate seems to be a simple, effective and safe treatment of warts. recommendations: further studies are recommended to estimate cellular zinc level and compar it with serum zinc level. Also topical zinc sulfate solution should be evaluated in patients with warts with slightly reduced serum zinc level.

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