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Evaluation of serum selenium levels in patients with multiple warts: a case–control study in the north of Iran

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Background
Some micronutrients including selenium (Se) have immunoregulatory effects in the body. Our hypothesis was that decreased serum Se levels could be associated with some degree of immunodeficiency and increased chance of multiple cutaneous warts.
Objective
To measure serum Se levels in patients with multiple cutaneous warts and healthy participants to verify its inhibitory role in cutaneous warts.
Patients and methods
A case–control study was conducted on 136 participants: 68 cases with multiple cutaneous warts and 68 age-matched and sex-matched healthy controls. Collected data were age, sex, number, duration, and clinical type of the warts. Blood samples were taken from all participants for the evaluation of serum Se level. Se level was measured with atomic absorption method.
Results
Median of the Se level was significantly lower in patients with multiple warts compared with healthy controls ($P<0.05$), but the frequency of Se deficiency was not significantly different in the two groups. There was not any association between Se level and number of warts, but it was significantly lower in palmoplantar warts compared with genital warts.
Conclusion
A significant decrease in median Se level in patients with multiple warts even without Se deficiency may cause some decline in immune system against papillomaviruses. Lack of Se deficiency in the north of Iran may have led to nonsignificant differences in the frequency of Se deficiency in the two groups.

Keywords:
immune system, selenium, wart

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Introduction

Cutaneous warts are usually self-limiting lesions in immunocompetent patients, especially in children, which develop due to human papillomavirus (HPV) infection [1,2]. Cellular immune system has a major role in the inhibition of HPV proliferation in epidermal cells. In immune-deficient patients multiple, larger, and resistant warts are more common [3,4]. Selenium (Se) is a micronutrient that contributes to the structure of selenoproteins, such as selenocysteine. It has an anti-oxidative effect and enhances humoral and cellular immunity [5,6].

Normal immune system especially in adult cases usually controls HPV infections but dysregulation of the immune system in atopic dermatitis or downregulation of the immune system especially in organ-transplanted patients could be associated with recalcitrant warts. Definitive reasons for immune failure against HPV infection in adult patients are not clear [1,7,8].

Oxidative stress effects, free radical oxygen generation, and decreased levels of antioxidants in the body have been incriminated in the pathogenesis of cutaneous viral diseases. Selenoproteins including glutathione peroxidase as anti-oxidative agents could effectively protect human cells against reactive oxygen and nitrogen in the body. Also, some micronutrients such as Se and zinc have essential roles in the regulation of immune system including T-lymphocytes, macrophages, natural killer cells, Langerhans cells, and neutrophils. They also reduce the risk of cancers and oxidative stress effects [6,9–11].

De Luca *et al.* [3] prescribed an oral supplement that consists of coenzyme Q10, Se, vitamin E, and methionine for 180 patients with chronic and

recurrent HPV infections in addition to cryotherapy. They showed it was associated with better improvement than cryotherapy alone. Vitamin C converts selenite composition to an inactive form of Se, but vitamin E has synergistic effect with Se composition [12]. Prescribing Se supplement even with normal serum Se levels results in the functional upregulation of the immune system. Also, Se has protective effects against HIV, depression, autoimmune diseases, diabetes, atherosclerosis, viral hepatitis, and herpes simplex virus [6,10].

Antioxidants and supplements such as zinc, Se, magnesium, and copper have been used as an adjuvant therapy for viral diseases including cutaneous warts [3,13,14]. We could not find any previous study about the evaluation of serum Se status in patients with multiple cutaneous warts, so this research was designed to evaluate the serum Se level in patients with multiple warts.

Patients and methods

Participants and study design

This study was designed as an age-matched and sex-matched case–control study performed during 9 months (November 2017–June 2018).

This study included 136 volunteers, 68 cases with multiple cutaneous warts and 68 healthy controls without wart, who were randomly selected from our patients who visited for aesthetic reasons in the outpatient clinic. The final sample size was calculated after a primary pilot study. Both groups were frequency matched in age groups (±10) (18–27; 28–37; . . . ; 58–67 years). All patients aged more than or equal to 18 years who did not meet our exclusion criteria and had consent for body examination and doing laboratory evaluation were included.

We excluded some cases as follows: age less than 18 years, mucosal warts, no consent for doing laboratory evaluation, any condition that can change serum Se level such as abnormal diet (vegetarian, ketogenic, etc.), pregnancy or lactation, smoking, alcoholism, underlying malignancy, thyroid dysfunction, inflammatory bowel disease, autoimmune skin diseases, nutritional supplements, and drug history of cisplatin, clozapine, corticosteroids, valproic acid, gold salts, oral contraceptive pills, previous chemotherapy, and immunosuppressive agents [5,15–18].

Examination of the patients was conducted according to the Declaration of Helsinki 2013 principles with informed consent. This research project was approved by the Ethics Committee of our University of Medical Sciences in 2018 (Approval Code: 1396.279).

Multiple cutaneous warts were defined as more than five cutaneous warts [7] and clinically diagnosed by an individual dermatologist without skin biopsy. Collected data were age and sex of participants, number, clinical types of cutaneous warts (common, plane, palmoplantar, and genital warts), and duration of the lesions in the patients' group. Serum Se levels were evaluated for both groups. The Se level was assessed in venous blood samples in an individual laboratory by the Graphite Furnace Atomic Absorption Spectrophotometry technique; PG instrument, AA500, United Kingdom. Determination of Se in serum was done in three steps using a Se hollow cathode lamp 196.5 nm and D2 background lamp; first step: extraction of the sample by triton x-100 and HNO_3 6 M, second step: sample centrifuge, third. step: 10 µl sample injection and modifier injection.

Normal serum level for Se has been defined as 46–143 µg/l, but Se level more than or equal to 90 µg/l is essential for optimal saturation of selenoproteins in humans [19].

Statistical analysis

Quantitative variables with normal distribution were described using mean and SD and variables without normal distribution were described using median (minimum–maximum). Qualitative data were reported by number and percentage. Quantitative variables with normal distribution in subgroups were evaluated using kurtosis, skewness, Q-Q plot, box plots, and Shapiro–Wilk test. For the comparison of frequencies, the χ^2 test or Fisher's exact test was used and for the comparison of continuous variables. Mann–Whitney test was applied in both groups. For determining the serum Se level considering age, sex, duration of the disease, clinical subtypes, and numbers of warts in each group, Mann–Whitney test, Kruskal–Wallis, one-way analysis of variance, and Tukey test were used. Spearman's test was used for studying the correlation between quantitative nonparametric variables. All statistical tests were performed in version 18.0. (SPSS Inc., Chicago, Illinois, USA). All P values were two sided; significance level was set at P value less than 0.05.

Results

A total of 68 cases with multiple warts and 68 healthy controls without warts with a mean age of 31.85

Table 1 Age and sex characteristics of participants

Variables	Median (minimum–maximum)/[*n* (%)]		*P* value
	Without warts (*N*=68)	With multiple warts (*N*=68)	
Age (year) [median (minimum–maximum)]	28 (18–65)	31.5 (18–64)	0.977*
Age groups (year) [*n* (%)]			
18–27	24 (35.3)	24 (35.3)	
28–37	25 (36.8)	25 (36.8)	
38–47	14 (20.6)	14 (20.6)	>0.999**
48–57	3 (4.4)	3 (4.4)	
58–67	2 (2.9)	2 (2.9)	
Sex [*n* (%)]			
Male	25 (36.8)	25 (36.8)	>0.999***
Female	43 (63.2)	43 (63.2)	

*Mann–Whitney test. **Fisher's exact test. ***χ^2 test. *P* value >0.05 is considered statistically non significant.

Table 2 Comparison of median selenium level in patients with and without multiple warts

Groups	Number	Selenium level (μg/l) [median (minimum–maximum)]	*P* value
Without warts	68	93.4 (43–143)	
With multiple warts	68	85.5 (38–141)	0.045*
Total	136	91 (38–143)	

Mann–Whitney test. *P* value <0.05 is considered statistically significant.

Table 3 Comparison of mean selenium levels in subgroups with different numbers and clinical types of warts

Subgroups with different numbers and clinical types of warts	Number of cases	Mean level of Se±SD	*P* value
Number			
6–10	20	90.25±23.75	
11–20	20	81.45±22.57	0.462
>20	28	87.94±23.45	
Clinical types			
Palmoplantar	13	72.59[a]±25.63	
Common	12	84.50[ab]±24.90	0.012*
Plane	26	86.16[ab]±18.51	
Genital	17	99.91[b]±21.22	

One-way analysis of variance test. *P value < 0.05 is considered statistically significant.

Table 4 Comparison of selenium level in patients with and without multiple warts

Selenium level	Patients without wart (*N*=68) [*n* (%)]	Patients with multiple warts (*N*=68) [*n* (%)]	Total (*N*=136) [*n* (%)]	*P* value
Lower than normal (<46 μg/l)	1 (33.3)	2 (66.7)	3 (2.2)	>0.999*
Normal (46–143 μg/l)	67 (50.4)	66 (49.6)	133 (97.8)	
Suboptimal (<90 μg/l)	29 (43.9)	37 (56.1)	66 (48.5)	0.170**
Optimal (≥90 μg/l)	39 (55.7)	31 (44.3)	70 (51.5)	

*Fisher's exact test. **χ^2 test. *P* value >0.05 is considered statistically non significant.

±10.58 were enrolled in this study. Mean age and sex distribution of the participants were not significantly different in two groups and were matched (Table 1).

Median Se level in cases with multiple warts was significantly lower than the healthy group (*P*=0.045) (Table 2), but comparison of mean Se levels in subgroups with different numbers of warts showed no significant difference (Table 3).

There was no significant difference in the frequency of Se deficiency (<46 μg/l) or suboptimal levels of Se (<90 μg/l) between the two groups (Table 4).

Pairwise comparisons using Tukey test showed significant differences in the mean level of Se in patients with palmoplantar warts compared with genital warts (*P*=0.012, one-way analysis of variance test). Palmoplantar wart group had a

lower level of Se (72.59±25.63 µg/l) and the genital wart group had a higher level of Se (99.91 ±21.22 µg/l) compared with the common wart and plane wart groups (Table 3).

Median duration time of wart infection in patients with multiple warts was 12 months (minimum: 2 months–maximum: 120 months).

There was no significant correlation between duration of warts and serum Se level (r=–0.116, P=0.345, Spearman's correlation coefficient).

Discussion

In the current study, the median Se level in cases with multiple warts was significantly lower than the control group. Se reinforces both innate and acquired immune systems. The highest amount of Se in the body is used in the reticuloendothelial system including the liver, spleen, and lymph nodes, so Se has a key role in humoral and cellular immunity [6].

There were only three cases of Se deficiency (<46 µg/l) in our participants with no significant difference in the two groups. The Se value in blood is strongly associated with a nutritional diet. Beans, nuts, oats, garlic, fish, and meat are rich reservoirs of Se. Se deficiency is mainly seen in regions with Se-poor soil and water. There is no association between serum Se level with age, sex, and BMI [20,21]. In general, the mean Se level of soil in Iran is lower than the worldwide value. The Se level of soil in Iran is lower than the nutritional products but in previous studies in the neighboring provinces of our province, all participants had a serum Se level of more than 90 µg/l (optimal level), which shows that there is no Se deficiency in the Northern Provinces of Iran, probably due to a diet rich in fish and garlic in these areas [19,22].

In this study, patients with palmoplantar warts had the lowest Se level compared with other clinical types of cutaneous warts. Probably poorer therapeutic responses in this group could be explained by this finding.

In spite of our initial impression, there was no correlation between numbers of cutaneous warts in the case group and serum Se level in our study. So, the preventive role of Se could be questionable.

Se has a protective effect against some cancers such as cervical cancer, which mainly develop due to HPV infections, but it cannot protect against skin cancers [6,10]. Although Se is an activator agent for Langerhans cells and it has been considered as a defensive agent against various cancers, there are paradoxical reports in this regard; for example, Dreno *et al.* [23] showed that Se supplement did not prevent HPV infections and skin cancers in organ transplant recipients. They showed that Se supplementation had no protective effect against basal cell carcinomas in organ transplant recipients and some patients had an increased risk of squamous cell carcinoma. Se supplementation has not had any protective effect against skin cancers in patients with a high Se concentration and should not be prescribed. Also Orozco-Topete *et al.* [11] mentioned that there was no association between the development of cutaneous warts and malnutrition. Interestingly, El-Komy *et al.* [24] found that Se level in toenails of patients with multiple cutaneous warts was significantly higher than the control group and levels of Se did not correlate with the number or duration of warts. Measurement of Se level in human toenails reflects the status of this element over the past several months. These findings may raise questions about the protective role of Se against HPV infection. But it has been proposed that other trace elements such as mercury and arsenic could antagonize the immune-regulatory effects of Se and levels of these toxic elements should be evaluated in these patients [25].Our research was a small sample-sized case–control study with a low frequency of Se deficiency in our province. Also, we did not evaluate levels of toxic elements or other essential micronutrients in our participants. So, we cannot conclude about the role of Se supplement in multiple cutaneous warts and a further large-scale study is needed.

Se supplement might be considered for patients with Se deficiency, especially in recalcitrant palmoplantar warts that are more resistant to treatment. Future clinical and laboratory researches about the role of Se supplement may be helpful for better management of HPV infections.

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Conflicts of interest

There are no conflicts of interest.

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