

Zinc Level of Serum in Recurrent Vulvovaginal Candidiasis

¹M. Zangeneh, ²S.D. Siadat, ³M. Jamshidi, ¹M. Alijani, ¹B. Farhoudi and ¹M. Valizadeh

¹Department of Infectious Diseases, Islamic Azad University, Tehran, Iran

²Department of Bacterial Vaccines and Antigen Production, Pasteur Institute of Iran, Iran

³Department of Infectious Diseases, Hormouzan University, Tehran, Iran

Abstract: Zinc status has been shown to influence various cell-mediated immunologic mechanisms. These cell-mediated mechanisms are important in preventing mucocutaneous infections caused by *Candida albicans*. This study evaluated the relationship between zinc status and recurrent vulvovaginal candidiasis by comparing plasma zinc in 51 patients with recurrent vulvovaginal candidiasis and 50 control healthy age-matched women. The results indicated that zinc concentration in plasma in patients with recurrent vulvovaginal candidiasis and control group showed no significant difference between case and control group ($p = 0.605$), 4(8%) women of control group and 5(11/1%) women of patients group had zinc concentration lower than normal. Also, no significant difference between the mean plasma zinc concentration (case group $48-189 \mu\text{g dL}^{-1}$ and control group $57-120 \mu\text{g dL}^{-1}$) in the patient and control group ($87 \mu\text{g dL}^{-1}$, std 23.5, $74.9 \mu\text{g dL}^{-1}$, std $13 \mu\text{g dL}^{-1}$) ($p = 0.031$).

Key words: Zinc deficiency, vulvovaginitis, candida, serum, recurrent

INTRODUCTION

Candidal vulvovaginitis is a common cause of morbidity among post pubertal women sometimes prepubertal girl. Several factors may increase women risk for developing the disease, these are: diabetes mellitus, oral contraceptives, steroids, antibiotic treatment, immunodeficiency, previous surgery, wearing tight clothing, zinc deficiency, obtaining candida from sexual contact. Unfortunately, the majority of these patients lack well known predisposing factors (Erika, 2000; Reed, 1992). Although greater than 50% of women more than 25 years of age develop vulvovaginal candidiasis at some time, fewer than 5% of these women experience recurrent Vulvovaginal candidiasis (Vulvovaginal candidiasis is considered recurrent when at least four specific episodes occur in one year). There is still major controversy over predisposing factors of recurrent vulvovaginal candidiasis (Erika, 2000). However, alteration in humeral as well as cell-mediated immunity have been ascertained in some patients suffering from recurrent vulvovaginal candidiasis (Chipperfield and Evans, 1972; Fidel, 2005; Salvin *et al.*, 1987; Sobel, 1989; Witkin *et al.*, 1983, Witkin, 1986).

Recently, dietary intake has been hypothesized as playing a role in the development of candida infections.

Zinc, an essential trace element, has been shown to influence several cell-mediated immunologic mechanisms (Bohler *et al.*, 1994; Gunningh-Rundles and Cunningham Rundles, 1988; Reed, 1992; Salvin *et al.*, 1987; Space *et al.*, 2005). Edman *et al.* (1986) found significantly lower plasma zinc level in women with recurrent vulvovaginal candidiasis compared with the control group and conducted that mild zinc deficiency plays a role in the susceptibility of women to vulvovaginal candidiasis. As well as several other studies (Space *et al.*, 2005; Salvin *et al.*, 1987; Barbara *et al.*, 1989) have shown the relationship between zinc status and recurrent vulvovaginal candidiasis (Reed, 1992; Salvin *et al.*, 1987; Soll *et al.*, 1981). In addition, several *in vitro* investigation have shown that zinc concentration of culture media are directly related to growth of candida albicans, release of Migration Inhibitory Factor (MIF) *in vivo* and the presence of low rate of phagocytosis and killing by macrophages. These observations might imply notable effects on yeast adherence capacity and antifungal treatment results (Anderson and Soll, 1984; Bedell and Soll, 1979; Soll *et al.*, 1981). This study was performed to evaluate potential association between zinc concentration in plasma and recurrent vulvovaginal candidiasis in patients and healthy controls in order to, the hypotheses that the intake of zinc is associated with candida vulvovaginitis is tested.

MATERIALS AND METHODS

In this control study 51 women between 15-50 years (mean age 35.84±2.17) who had experienced at least 3 documented episodes of acute recurrent vulvovaginal candidiasis within the previous 12 months were included in the patients group after oral informed consent. Patients with ingestion of zinc supplements within 7 day, diabetes mellitus, oral contraceptives, steroids, antibiotic treatment, immunodeficiency, previous surgery could not be in the study and 50 healthy age-matched women served as a control group. None of the control subjects had ever suffered from vaginal candidiasis. From all case group vaginal smear and culture for candida were taken. For zinc determination 10 mL of blood were drawn in the morning, after an overnight fast from patients with vaginal candidiasis. Blood was centrifuged immediately for 15 min and the plasma was stored at -20°C until further analysis.

Zinc concentration were determined by Flame Atomic Absorption Spectrophotometry. The data analysis was done by computer SPSS program with use of chi-square (chi²) statistic method for analysis of significance. A p value < 0/05 was regarded as significant.

RESULTS

The results of zinc concentration in plasma in patients with recurrent vulvovaginal candidiasis and control group and age of cases are shown in Table 1 and 2. No significant difference could be found in number of patients with zinc deficiency in case and control group (p = 0.290), 4(8%) cases of control group and 5(11/1%) cases of patients group had zinc concentration lower than normal. Also, no significant difference could be found in the mean plasma zinc concentration (case group

48-189 µg dL⁻¹ and control group 57-120 µg dL⁻¹) between the patient and control group (87 µg dL⁻¹, std 23.5, 74.9 µg dL⁻¹, std 13 µg dL⁻¹ p = 0.031) Normal zinc plasma levels are 100±12 mcg 100 mL⁻¹ We did not find any positive correlation between the zinc concentration in plasma in either group.

DISCUSSION

Genital infection with *Candida* species is common in women, 75% of women will have at least one episode during their lives and some patients suffer frequent recurrences or chronic infection. After therapy negative vaginal culture turn positive for *C. albicans* within 30 days in 20-25% of patients. Small numbers of the microorganisms persist, however, within the vaginal lumen, generally in numbers too small to be detected by conventional vaginal smear or culture. Relapse due to non eradication is supported by the fact that short time recurrences are usually of the same biotype (Erika, 2000; Kubota, 1998; Odds, 1987a, b; Sobel, 1989; White *et al.*, 1991). Zinc has been known to be an essential nutritional element for more than 100 years. Zinc serves as a cofactor for more than 70 different enzymes including carbonic anhydrase, alkaline phosphatase, lactic dehydrogenase and both RNA and DNA polymerase. Zinc facilitates wound healing, helps maintain normal growth rates, normal skin hydration and the senses of taste and smell The amount of zinc available varies with alimentary, which varies with different diets, the percentage absorbed by the digestive tract and the excretion rate. It has been suggested that zinc is absorbed primarily through the small intestine by active as well as passive transport mechanisms. Interactions between zinc and other metal cations and organic compound in the intestinal lumen dramatically affect absorption (Bohler *et al.*, 1994; Gunningham and Cunningham, 1988; Prasad *et al.*, 1963). Zinc deficiency influence several cell-mediated immunologic mechanisms such as reduction of skin test reaction, thymus atrophy, T cell and CD4 T helper and natural killer cells decrease, monocytes and CD3 increase (Fidel, 2005; Gunningham-Rundles and Cunningham, 1988). In 1963 Prasad, for the first time reported increased susceptibility to infection in association with primary zinc deficiency. Moynahan in (1973) discovered that acrodermatitis entropathica, an autosomally recessive disorder of zinc metabolism is associated with an increased incidence of infection, primarily with *candida*. Accumulated data from human and animal studies suggest a major relationship between zinc deficiency and impairment of different immune functions. In Edman *et al.* (1986) reported that mild zinc

Table 1: Age of cases

		Frequency	Valid percent	Cumulative percent
Valid	< 10Y	0	0.0	0.0
	10-20 Y	2	4.1	4.1
	21-40 Y	28	57.1	61.2
	> 40 Y	19	38.8	100.0
	Total	49	100.0	
Missing	System	2		
Total		51		

Table 2: Group serum zinc crosstabulation

Group	Case	Count	Serum zinc		
			Low	Normal	Total
Group	Control	Count	5	46	51
		% within Group	9.80%	90.20%	100%
Group	Case	Count	4	46	50
		% within Group	8.00%	92.00%	100%
Total	Control	Count	9	92	101
		% within Group	8.91%	91.09%	100%

deficiency might play a role in the susceptibility to recurrent vulvovaginal candidiasis. They found significantly lower plasma zinc level in women with recurrent vulvovaginal candidiasis than control subjects. Bohler in 1994 could not confirm these results, as patients and control group exhibited comparable plasma zinc levels. In Salvin *et al.* (1987) showed, mice strain on normal diet are defective in some aspects of cellular immunity, as evidenced by their susceptibility to infection with *Candida albicans*, their failure to release of circulating Migration Inhibitory Factor (MIF) *in vivo* and the presence of low rate of phagocytosis and killing by peritoneal macrophages. When the mice were fed a high-zinc diet for 4 weeks and then treated daily with prothymosin alpha, an increase occurred in resistance to infection with *C. albicans*. In Spacek (2005) in a cohort study, concentrations of metals in 44 patients with RVVC and 30 healthy age-matched women measured and compared. In our study we could not confirm these results, as patients and control group showed comparable plasma zinc levels. The concentrations of serum Calcium (Ca), Magnesium (Mg) and iron (Fe) were measured photometrically, the Zinc (Zn) levels were determined using flame atomic absorption spectrometry. Although all measured metals were within normal ranges, the patients with RVVC had in contrast to the healthy controls significantly lower levels of serum Ca, Mg and Zn and insignificantly higher levels of Fe. These relative changes may contribute to the development of attacks in patients with RVVC.

We can not support Edmonds conclusion that increased susceptibility to recurrent vulvovaginal candidiasis is caused by plasma zinc deficiency. Non eradication of *C. albicans* is one of the most discussed causes of recurrent vulvovaginal candidiasis. After therapy negative vaginal culture turn positive for *C. albicans* within 30 days in 20-25% of patients. Small numbers of the microorganisms persist, however, within the vaginal lumen. Relapse due to non eradication is supported by the fact that short time recurrences are usually of the same biotype (Erika, 2000; Kubota, 1998; Sobel, 1989).

It has been demonstrated that zinc considerably participates in the growth and morphogenesis of *C. albicans*. Evidence has been presented that cells do not stop multiplying because of the depletion of nutrients from the supporting medium, but owing to the depletion of zinc. In our study, we could not confirm relationship between zinc deficiency and VVC, as patients and control group exhibited comparable plasma zinc levels.

CONCLUSION

In conclusion, our study were not able to confirm statistically zinc deficiency is a risk factor in recurrent vulvovaginal candidiasis, According to the available data of other study, the zinc level of cervicovaginal secretion might influence recurrent vulvovaginal candidiasis. Furthermore, future study need to support the hypotheses that zinc deficiency in cervicovaginal secretion is risk factor for recurrent vulvovaginal candidiasis.

REFERENCES

- Anderson, J. and D.R. Soll, 1984. Effects of zinc on stationary-phase phenotype and macromolecular synthesis accompanying outgrowth of *Candida albicans*. *Infect. Immun.*, 46: 13-21.
- Bedell, G.W. and D.R. Soll, 1979. Effects of low concentrations of zinc on the growth and dimorphism of *Candida albicans*; evidence for zinc-resistant and sensitive pathways for mycelium formation. *Infect. Immun.*, 26: 348-354.
- Bohler, R. *et al.*, 1994. Zinc levels o serum and cervicovaginal secretion in recurrent vulvovaginal candidiasis . *Genitourin. Med.*, 70: 308-310.
- Chipperfield, E.J. and B.A. Evans, 1972. The influence of local infection on immunoglobulin formation in the human endocervix. *Clin. Exp. Immunol.*, 11: 219-23.
- Edman, J. *et al.*, 1986. Zinc status in women with recurrent vulvovaginal cadidiasis. *Am. J. Obstet. Gynecol.*, 155: 1082-1085.
- Erika, N.R., 2000. Treatment of Recurrent Vulvovaginal Candidiasis. *American Family Physician*, University of MissouriColumbia School of Medicine, Columbia Vol. 61, No. 11.
- Fidel, P.L. 2005. Immunity in vaginal candidiasis. *Curr. Opin. Infect. Dis.*, 18: 107-111.
- Gunningham Rundles, S. and W.F. Cunningham- Rundles, 1988. Zinc modulation of immune response. In Chandra RK Ed. *Contemporary Issue in Clinical Nutrition II, Nutrition and Immunology* New York Alan R Liss, pp: 197-210.
- Kubota, T., 1998. Chronic and recurrent vulvovaginal candidiasis. *Nippon Ishinkin Gakkai Zasshi*, 39: 213-218.
- Odds, F.C., 1987. Epidemiology of vaginal *Candida* infection: Significance of numbers of vaginal yeasts and their biotypes. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 25: 53-66.

- Odds, F.C., 1987. Candida infections; Crit. Rev. Microbiol., 15: 1-5.
- Prasad, A.S. *et al.*, 1963. Zinc metabolism in normals and patients with the syndrome of iron deficiency anemia, hypogonadism and dwarfism. J. Lab. Clin. Med., 61: 537-539.
- Reed, B.D. *et al.*, 1989. The association between dietary intake and reported history of Candida vulvovaginitis. J. Family Practice.
- Reed, B.D., 1992. Risk factors for Candida vulvovaginitis. Obstet Gynecol Surv. Department of Family Practice, University of Michigan Medical School, 47: 551-560.
- Salvin, S.B. *et al.*, 1987. The effect of dietary zinc and prothymosin alpha on cellular immune responses of RF/J mice. Clin. Immunol. Immunopathol., 43: 281-280
- Sobel, J.D., 1989. Pathophysiology of Vulvovaginal Candidiasis. J. Report. Med., 34: 527-580.
- Soll, D.R. *et al.*, 1981. Zinc and the regulation of growth and phenotype in the infectious yeast Candida albicans. Infect. Immunol., 32: 1139-1147.
- Space, K.J. *et al.*, 2005. The serum levels of calcium, magnesium, iron and zinc in patient with vulvovaginal candidiasis during attack, remission and in healthy controls. Mycoses, 48: 391-395.
- White, D.J. *et al.*, 1991. Recurrent vulvovaginal candidosis. Int. J. STD. AIDS., 2: 235-239.
- Witkin, S.S. *et al.*, 1983. Inhibition of Candida albicans induced lymphocyte proliferation by lymphocytes and sera from women with recurrent vaginitis. Am. J. Obstet. Gynecol., 147: 809-812.
- Witkin, S.S., 1986. A macrophage defect in women with recurrent Candida vaginitis and its reversal *in vitro* by prostaglandin. Am. J. Obstet. Gynecol., 155: 790-795.