EFFECT OF ZINC TREATMENT ON GONADAL DYSFUNCTION IN HEMODIALYSIS PATIENTS

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SUMMARY : Zinc deficiency may account for the persistence of gonadal dysfunction in a majority of uremic men despite adequate dialysis treatment. Twenty nine hemodialyzed men having sexual dysfunction were selected and randomly divided into control and treatment groups (12 and 17 patients) respectively. Zinc acetate at 200 mg and $CuSO_4$ 2 mg were given orally per day for 8 months to patients in the treatment group. At the end of the study, significant increases in the mean serum levels of serum zinc (54 ± 2 µg/dL to 76 ± 3 µg/dL p<0.01), serum copper (89 ± 3 µg/dL to 123 ± 7 µg/dL p<0.01) and testosterone (4.8 ± 0.39 ng/mL to 6.2 ± 0.45 ng/mL p<0.01) were observed. A significant increase in follicle-stimulating hormone-FSH (10.0 ± 1.80 mIU/mL to 6.0 ± 1.34 mIU/mL p<0.01) and in luteinizing hormone-LH (16.0 ± 3.17 mIU/mL to 6.7 ± 1.42 mIU/mL p<0.01) were observed in the zinc receiving group. Eight of 17 patients in the treatment group revealed an improvement in sexual activities (p<0.05), while no alterations were observed in their counterparts in the control group. Likewise no significant changes of the trace elements and hormones were not found in the latter group.

Key Words : Hemodialysis, zinc deficiency, gonadal dysfunction.

INTRODUCTION

Abnormalities in sexual function are not uncommon among patients with end stage renal disease (ESRD). Sexual dysfunction does not improve after regular hemodialysis (HD) treatment (I-5). Even though the cause of impotence in uremic men is not definitely known, the presence of psychosocial instability (6), gonadal dysfunction (7), and uremic toxins (8) have been implicated. Some authors have already proposed that these findings, which frequently develop as the clinical condition deteriorates, may be secondary to zinc deficiency (4, 9-11).

Zinc therapy has been applied to ESRD patients by several investigators. Their results, however, have not been uniformly successful (12,13). On the contrary, some others have reported significant improvement in sexual dysfunction after zinc treatment (4,9,11). We have also observed significant zinc deficiency in patients undergoing regular hemodialysis in our center. Most of them have described various sexual dysfunctions (14). These observations suggest that perhaps zinc therapy may be valuable for gonadal dysfunction as well as for the treatment of zinc deficiency signs and symptoms. We therefore, decided to attempt correction of zinc deficiency and then evaluate the response of the patients.

MATERIALS AND METHODS

Twenty-nine ambulatory, stable male patients undergoing chronic hemodialysis for more than 18 months and with sexual dysfunction were chosen for the study. They were randomly selected into two groups, the first being the treatment group (17 patients) and the second the control group (12 patients). The mean ages were 41.1 ± 2.4 years (range 20-58 years) for treatment group and 41.7 ± 2.0 years (range 21-56 years) for control group. None of these had metabolic disease, polyneuropathy nor a history which could possible cause sexual dysfunction. All patients were receiving antacids, multivitamins and iron prepara-

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tions before and during study. Their diet contained 1 gram of protein / kg/day.

All patients had normal secondary sexual characteristics and none revealed gynecomastia. All patients had been sexually active before the onset of HD. Twenty-two of these patients were married and 5 were single, two were divorced. Twenty-one patients had fathered one to seven children, all of which were born before the beginning of HD. In general, dialysis was begun when the creatinine clearance was less then 10 ml/min. Polyneuropathy had verified by using electromyography before the study.

The clinical and biochemical features of the two groups are shown in Table 1. Comparison of patients in the treatment group with those in the control group showed no significant differences in age, duration of dialysis and other parameters before the study. None of these had been given methildopa, beta blocking agents and erythropoetin before and during study.

In the treatment group each patient was given Zinc acetate 100 mg, and $CuSO_4$ 1 mg, twice a day for 8 months. Blood samples were drawn at the initiation of the study, before dialysis, and at the end of the study, more than 12 hours after the last zinc doses and meal. Blood samples were centrifuged and serum was separated. Serum zinc, copper and red blood cell zinc (RBZn) were determined by using an atomic absorption spectrophotometer. (Alpha 4) Serum FSH, LH, testosterone, prolactin, cortisol, dihydro-epiandrosteron (DHEA) and sex hormone binding globulin (SHBG) were determined by using the Behring radial immunodiffussion plaques.

Each patient was inquired concerning his sexual activity at the beginning and at the end of study. The questionnaire included information on the patient's marital status, number of children, interest in sexual activity, frequency of intercourse, ability to have or maintain an errection etc.

Table 1: Initial clinical and laboratory data (Mean ± SE) of the two groups.

	Treatment Group	Control Group	P
Age. yrs	41.1±2.4	41.7±2.0	>0.05
Duraiton of Hd-month	52.2±7.4	48.0±6.0	>0.05
Urea (20-54 mg/dL)	132±10	135±13	>0.05
Creatinin (0.01-1.7 mg/dL)	8.9±1.2	9.0±1.3	>0.05
SHBG (10-73 nmol/L)	50±4.7	57±5.5	>0.05
S. Protein (6-8.2 g/dL)	6.8±1.46	6.9±0.18	>0.05
S. Albumin (4-5.6 g/dL)	4.6±0.52	4.3±0.48	>0.05
S. Transferrin (2-4 g/L)	2.5±0.52	2.6±0.34	>0.05
Hemoglobuline (14-18 g/dL)	9.4±2.07	9.1±0.49	>0.05

Normal values in parenthesis

Table 2: Laboratory findings (Mean±SD) in zinc-receiving group (n=17).

	Before Treatment	After Treatment	P
S. Zinc (100-110 ug/dL)	54±2.01	76±3.59	<0.01
RBZn (1500-1800 ug/dL)	1248±103	1322±118	>0.05
S.Cu (110-130 ug/dL)	89±3.54	123±7.28	<0.01
FSH (2-20 mIU/ml)	10.0±1.80	6.0±1.34	<0.01
LH (0.4-3.7 mIU/mL)	16.0±3.17	6.7±1.42	<0.01
Testosteron (2.7-10.7 ng/mL)	4.8±0.39	6.2±0.45	<0.01
Prolactin (3-17 ng/mL)	23.0±1.94	22.8±2.03	>0.05
DHEA (80-560 Ug/dL)	163±21	153±23	>0.05
Cortisol (5-25 ng/dL)	13.9±2.12	13.8±1.89	>0.05

Normal values are indicated in parenthesis

RESULTS

The clinical and biochemical features of the two groups are shown in Table 1. The results were compared statistically and no changes were found at the initiation in all parameters of the two groups. It is important to note that both serum zinc and copper levels of the two groups were found to be significantly lower than the normal at the beginning of the study.

In the treatment group, mean serum zinc and copper significantly increased during the study, but still remained lower than the normal value at the end ($p<0.01$). Red blood cell zinc was observed to have slightly increased, but was not significantly above the baseline value. Serum testosterone levels increased significantly ($p<0.01$) while FSH and LH decreased ($p<0.01$) after treatment. In this group, serum prolactin, DHEA and cortisol levels did not reveal

Table 3: Laboratory findings (Mean ± SE) in control group (n=12).

	Before Study	After Study	P
Serum Zinc Ug/dL	59±3.19	58±3.04	>0.05
RBZn Ug/dL	1263±110	1351±124	>0.05
Serum Cu Ug/dL	96±4.19	106±4.93	>0.05
FSH mIU/ml	9.1±1.94	8.7±1.79	>0.05
LH mIU/mL	14.3±2.97	12.9±2.38	>0.05
Testesteron ng/mL	5.3±0.48	5.2±0.54	>0.05
Prolactin ng/mL	19.2±1.85	21.6±2.10	>0.05
DHEA Ug/dL	147±24.64	123±19.84	>0.05
Cortisol ng/dL	15.7±1.88	13.2±1.71	>0.05

Table 4: Sexual function history before and after study in two groups.

	Treatment group (n:17)		Control group (n:12)	
	Baseline	After study	Baseline	After study
Impotence	15+	7	11	11
Decreased libido	7	3	6	7
Decreased frequency of intercourse	17+	9	12	12

+ : p<0.05 from baseline.

any significant alterations while on zinc therapy (Table 2).

In the control group there were no differences in all parameters between baseline and at the end of the study, (Table 3).

In the treatment group 8 patients of 17 described improvement of impotency and frequency of intercourse, 4 patients described increase of libido. In contrast, one of the 12 symptomatic patients in the control group experienced any improvement in sexual potency at the end of the study period. Sexual satisfaction, libido and frequency of intercourse slightly improved in patients receiving zinc ($p<0.05$) but not in patients of the control group. A significant relation between serum zinc and testosterone ($p<0.01$) was present before and after the study in two groups. No correlation however, was observed between serum zinc and testosterone levels and sexual potency before and after study. There was also no correlation between improvement sexual potency and duration of dialysis (Table 4).

DISCUSSION

Zinc is an essential trace element for life. Growth retardation, testicular atrophy, abnormalities of gestation and olfaction and impaired wound healing have been associated with zinc deficiency in humans and animals (10). Similar manifestations are also present in uremic patients and are not improved by dialysis treatment (15). Subnormal plasma and serum zinc levels have been observed in uremic patients (4,15-17). We have observed that not only zinc but also serum copper levels are low in hemodialysis in HD patients (14).

The cause of zinc deficiency is not well known in uremic patients. Protein calorly malnutrition, malabsorption, decreased bioavailability of zinc in the diet, dietary habits (10,16,18) drug interaction with zinc (19) and increased urinary excretion of zinc (20) as factors underlying zinc deficiency in uremia. It has been observed that zincuria is directly connected to proteinuria in patients with nephrotic syndrome (21). Prehn (22) has reported that the observed a relationship between zinc deficiency with the progress of chronic renal failure.

Whether or not hemodialysis patients are loosing a significant amount of zinc into the dialysate has been investigated. An important loss of zinc by this route has not been observed (23). We have also found no significant zinc and copper loss from patient into the dialysate (24). Lindeman *et. al.* (20) have reported that zinc is bound to alfa-2 micro-globulin in plasma which cannot penetrate to through dialyzes.

Gonadal dysfunction has been consistently found in uremic males (1,4,5,7,8,11,25). The role of zinc in the gonadal dysfunction of these patients is not well established. Zinc deficient animals develop impairment of testicular growth and have low serum testosterone and elevated serum FSH and LH levels (10). Similar hormonal changes are seen in uremic patients having HD treatment (1,5,7,8,11). Testosterone deficiency may lead frequently to impotence an decreased libido and sexual dysfunction in these patients (10,11). Testosterone deficiency may be due to either hypothalamic-pituitary dysfunction or direct uremic toxicity on reproductive tissues (25-27).

The role of zinc in testicular testosterone production is not clear. However, zinc is essential for nucleic acid synthesis and activities of many enzymes (10). Zinc concentration, which is normally high in prostate, testis and kidneys, is reduced in uremia (28). Zinc deficiency may cause abnormalities in nucleic acid synthesis and protein many factoring. The predominant role of zinc in testicular function probably has an effect on cellular proliferation (1). The relationship between zinc deficiency and gonadal dysfunction has been investigated in hemodialysis patients. Rodger *et. al.* (13) administered 50 mg of elemental zinc per day orally and after 6 moths treatment, he observed no significant sexual alteration. Brook *et. al.* (12) claimed a significant rise within 6 weeks in serum zinc as a result of adding zinc-chloride into dialysate. No return of sexual function, however, was observed. Zetin and Stone (29) have reported no changes in sexual activity and in serum zinc levels after adding zinc-chloride to the dialysate. Hosokawa and Yoshida (30) have found increasing serum zinc after erythropoetin treatment in hemodialysis patients, but they did not report knowledge about the gonadal and sexual functions. Mahajan *et. al.* (4,11) have reported an elevation in serum testosterone levels and a reduction in FSH, LH levels in ureic men after oral zinc treatment. A significant increase in sexual activity and an improvement

in impotency have also been observed during their study. Antoniou *et. al.* (9) reported similar results. Our observations are in particular agreement with those of the last two authors, despite the fact that the serum zinc levels still remained below normal. This may indicate that complete return of these values to normal may lead to better results in gonadal dysfunction.

In our study, the patients could not tolerate oral zinc administration and they did not take more than 50 mg elemental zinc, therefore, at the end of the study period serum zinc levels increased significantly but still remained under normal values. On the other hand the mean increase in RBZn value was still statistically insignificant.

Our observations support the findings of earlier investigators who concluded that zinc deficiency may play an important role in the development of sexual dysfunction (4,9,11). We believe that the available evidence adequately supports that sexual dysfunction may be effectively reversed by oral zinc treatment. It is important to note, however, that the dose and the duration of zinc administration should be sufficient to provide the necessary return of serum and tissue levels to normal values.

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