Effect of Zinc Administration on Plasma Testosterone, Dihydrotestosterone, and Sperm Count

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The effects of zinc therapy on plasma testosterone (T), dihydrotestosterone (DHT), and sperm count were studied in 37 patients with idiopathic infertility of more than five years duration. In the first group (T < 4.8 ng/ml; 22 patients), T and DHT rose significantly after oral administration of zinc, as did the sperm count. Nine wives became pregnant, six within 3 months and three within 2 months of a second trial. In the second group (T ≥ 4.8 ng/ml; 15 patients), T and sperm count were unaffected by zinc, while DHT increased significantly. There was no conception observed. The rationale of this treatment and the significance of the results are discussed.

Key Words: Zinc therapy; Plasma androgens; Male infertility.

INTRODUCTION

Zinc appeared, for the first time, in biological literature one century ago when Raulin [17] showed that it is necessary for the growth of *Aspergillus niger* in culture and when Raoult and Breton [16] demonstrated its presence in human liver. In 1921, Bertrand and Vladesco [4] observed that the herring testes were considerably richer in zinc during the season of reproduction than in the resting season. Moreover, high concentrations of zinc were found in the testes and the accessory genital glands of various animals including man. Thus in view of these data, they suggested that zinc might play an important role in reproductive physiology in vertebrates. Prasad's study of zinc metabolism in geophagia [14, 15] brought evidence that certain cases of nutritional dwarfism with hypogonadism in man were associated with zinc deficiency and that zinc administration reversed both disorders.

Little is known about plasma zinc levels in human male infertility and no attempt has been made to treat oligozoospermia with this metal [8, 9].

MATERIALS AND METHODS

Thirty seven patients between 20 and 40 years of age with infertility of more than 5 years were selected according to the following criteria based on clinical history, examination and semen analysis:

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1. oligozoospermia under 25 million spermatozoa/ml and if over 15 million (4 cases) motility under 30%;
2. absence of gross malformations of the epididymis or the vas deferens,
3. absence of obstructive sequelae secondary to genital infection, and
4. wife with no detectable gynecological disorder.

The following determinations were carried out on blood plasma collected around 9 AM: zinc, testosterone (T), dihydrotesterone (DHT), FSH, LH, and prolactin. On account of the pulsatility and variability of these plasma levels, three to five assays were performed at 10-min intervals and the mean value determined.

The first patients were given 660 mg per day of zinc sulphate. Because of gastric intolerance, this dose was subsequently reduced to 120 mg twice per day during meals. After treatment for 40–50 days, the same laboratory investigations were performed again.

Zinc was assayed by atomic absorption spectrometry [7]. A double antibody radioimmunoassay was used for the determination of FSH, LH [19], and prolactin. In the latter technique the tracer was a purified preparation of human prolactin labeled with I^{125} [20] and the standard the NIH VLS N°1 preparation. The prolactin antiserum was obtained from Calbiochem and the immunosorbent from CIS. At the level of 10 ng/ml, intra- and interassay variability were 7% and 12%, respectively.

DHT and T were measured by radioimmunoassay after chromatography on celite microcolumn [18]. The antiserum used was raised in the rabbit injected with testosterone-3(O-carboxy-methyl)-oxime coupled to bovine serum albumin. The same antiserum was used for DHT determination since the cross-reaction with this steroid was 49% [11]. The Wilcoxon nonparametric rank test was used for statistical studies.

RESULTS

Patients were subdivided into two subgroups according to the basal plasma T level: group I (22 patients)—plasma T level below 4.8 ng/ml, and group II (15 patients)—T over or equal to that value. The mean and the range of sperm count, T, DHT, and zinc plasma levels in these two groups are shown in Table 1 before and after zinc administration. As expected, zinc increased after therapy although the increment was slight in a few cases. It was, however, difficult to assess in these cases whether or not some pills had been omitted.

In the first group, plasma T rose significantly ($p < 0.01$) and so did DHT ($p < 0.01$) and sperm count ($p < 0.01$) (Table 1). Nine wives became pregnant, six within 3 months of the first treatment and three in the course of a second attempt of the same treatment prescribed for 2 months after 6 months interruption. In the second group, plasma T did not rise significantly and sperm count was not affected by zinc administration. However, there was a significant increase of DHT ($p < 0.01$) (Table 1). The wives of these patients did not conceive. In both groups, baseline plasma levels of gonadotropins and prolactin were within the normal range and were unaffected by zinc therapy.

DISCUSSION

There is controversy concerning the relationship between idiopathic infertility and plasma T levels. These discrepancies are due to the fact that this disorder is not a disease but a syndrome with many causes, the most frequent being previous cryptor-

TABLE 1 Effects of Zinc Sulphate Therapy on Plasma Levels of Zinc, Testosterone, and Dihydrotestosterone and on Sperm Count in Oligozoospermic Patients

Parameter		Group I (N = 22)		Group II (N = 15)	
		Before	After	Before	After
Sperm count	range	0–24	0–78	0–25	0–170
(10^6/ml)	mean	8	20	7	19
		$p < 0.01$[a]		NS	
Zinc	range	0.80–1.50	0.92–2.10	0.73–1.26	1.00–2.33
(μg/ml)	mean	1.04	1.54	1.00	1.65
		$p < 0.01$		$p < 0.01$	
Testosterone	range	2.30–4.70	2.50–10.00	4.90–7.50	3.40–9.30
(ng/ml)	mean	3.50	5.40	6.00	6.50
		$p < 0.01$		NS	
Dihydrotestosterone	range	0.20–0.57	0.25–0.90	0.30–0.66	0.33–0.80
(ng/ml)	mean	0.38	0.50	0.48	0.57
		$p < 0.01$		$p < 0.01$	

[a]Wilcoxon test.

chidism, which is believed to be subsequent to a minor malformation of embryonic testes. Many unexplained cases of male infertility, even without a previous history of cryptorchidism, are likely to be the consequence of a genetic or rather an embryonic anomaly.

Patients with chromosomal abnormalities, metabolic disorders (diabetes, hyperlipidemia), serious emotional problems, and vascular disease were discarded from this study. Thus only patients with no obvious cause of their infertility were studied. However, cases with a previous history of cryptorchidism were not discarded.

There is no correlation between sperm count and basal plasma T level. The mean overall T level in oligozoospermia was, however, relatively low due to the high frequency of levels below 4.8 ng/ml. This value has been considered as critical because plasma T, when measured three times, is above this level in 93% of fertile men between 20 and 40 years of age and this in agreement with the study of Da Rugna [5]. Only special circumstances, like emotional stress, lower plasma T level. That is why indiscriminate studies in so-called normal men may display lower values.

It has been claimed that conception cannot be considered as an evidence of the improvement of the male infertility syndrome [6]. However, the difference between the results obtained in the two groups and concerning the number of pregnancies and the increase of sperm count and plasma T levels, seems to be consistent with the hypothesis that zinc administration may have been implied in this development. Assuming that there is a relationship between sperm count and zinc therapy, the mechanism of action of the latter remains to be established.

In some cases, conception was obtained within 4–6 weeks of zinc therapy while plasma T had already attained the normal range. These two facts might be related since it has been demonstrated that T acts upon spermiogenesis and epididymal function [10]

The mechanism of action of zinc is still unclear. Zinc is a structural component of more than twenty fundamental enzymes such as alkaline phosphatase, decarboxylase, 5α-reductase, dehydrogenase [13]. Moreover, zinc is essential for the regulation of the metabolic processes in the biosynthesis of RNA and DNA. Besides, it is found in high concentrations in the prostate, the testes, and seminal plasma. Availability of zinc influences the activity of some testicular enzymes. Thus zinc deficiency may alter the synthesis and metabolism of nucleic acids, proteins [21, 22] and hormones in these organs [23]. Animal studies have already shown that zinc deprivation reduces testicular RNA and DNA, depresses spermatogenesis, and elevates plasma FSH. Impotence in chronic renal failure is alleviated and plasma T increases under zinc therapy [1–3, 12].

Conversely to the fall of plasma zinc observed in acrodermatitis enteropathica and geophagia the patients studied did not demonstrate a clearcut zinc deficiency although most of plasma zinc levels were within the low normal range.

In conclusion, some cases of idiopathic male infertility with low plasma T levels can be successfully treated by oral administration of zinc. More studies are, however, needed to confirm these preliminary data.

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