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# ZINC AND THE STEROID ENDOCRINOLOGY OF THE HUMAN PROSTATE

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SUMMARY

The concentrations of zinc in the prostate are significantly lower in patients with carcinoma of the prostate than in normal control subjects. Although the mechanism responsible for the changes in zinc concentration in the pathological gland remains unexplained, there is now evidence that the metal controls a number of important biochemical functions in the prostate. The purpose of the present article is to review these metabolic functions and to evaluate the significance of zinc measurements in the diagnosis of carcinoma of the prostate.

## INTRODUCTION

Zinc is an important trace element involved in the growth and development of many organ systems. The metal is a normal constituent of a large number of enzymes and proteins and is found in high concentrations in the male accessory sex organs [1].

Attention was first drawn to the high zinc content of the human prostate by Bertrand and Vladesco[2] and subsequently confirmed by many other workers [3–6]. On average the normal human prostate contains about 6.84 $\mu$mol zinc per gram dry weight of tissue. This concentration is approximately ten times higher than in most other soft tissue with only human sperm exhibiting a greater concentration [3].

With the exception of Györkey *et al.*[7], most authors have reported similar levels of zinc in benign prostatic hypertrophy to those observed in the normal gland. These concentrations are, however, significantly lower in the carcinomatous tissue [6, 8–10].

## DISCUSSION

### *Glandular distribution of zinc*

Although the division of the human prostate into its various lobes remains controversial [11] attempts have been made to establish the concentration of zinc in the different parts of the gland. Györkey *et al.*[7] have demonstrated a fundamental difference in the distribution of the metal throughout the prostate and have observed variations which do not necessarily correlate with the anatomical division of the gland. Significant, however, are the observations made by Kerr *et al.*[5] and Maquinay *et al.*[12] showing an increase in zinc concentration towards the apex of the gland near the verumontanum. Radioautography and histochemical studies of administered $Zn^{65}$ revealed the presence of zinc mainly in the glandular epithelial cells [7, 13]; these do not, however, correlate with the epithelial content of the normal and hypertrophied tissue. In cancer cells the metal was present mainly in the nuclei but was not demonstrable in the cytoplasm [14].

### *The role of zinc in the prostate*

Lo *et al.*[15] demonstrated that the epithelial cells of the canine prostate are particularly sensitive to damage on the administration of the zinc chelating agent diphenyl-thiocarbazone (dithizone). The cellular damage is soon followed by an apparent atrophy. These abnormalities are, however, reversed following the administration of large doses of zinc salt and the restoration of zinc concentrations to their normal levels.

Although a fundamental distinction must be made between animal studies and experiments on human tissue, one cannot ignore the evidence derived from the dog experiments. Recent work on the human prostate now shows the importance of zinc in the following processes.

A. *Androgen concentration.* Testosterone is extensively metabolized in most androgen sensitive tissues both to non polar and polar derivatives. In the prostate, it has been suggested that the multiplication of epithelial cells is dependent on the formation of dihydrotestosterone (DHT) in the cytoplasm and on the subsequent incorporation of DHT into the cell nucleus [16–18]. Analysis of endogenous androgens in human BPH [18–20] revealed that DHT was markedly increased in the periurethral zone of the hyperplastic glands compared with analogous areas in normal tissues. Testosterone and 4-androstene-3,17-dione (androstenedione) maintained, on the other hand, their normal levels. In contrast to the previous observations, Habib *et al.*[19] demonstrated that the levels of testosterone in carcinomatous tissue were significantly raised whilst DHT remained constantly low (see Fig. 1). The mechanisms responsible

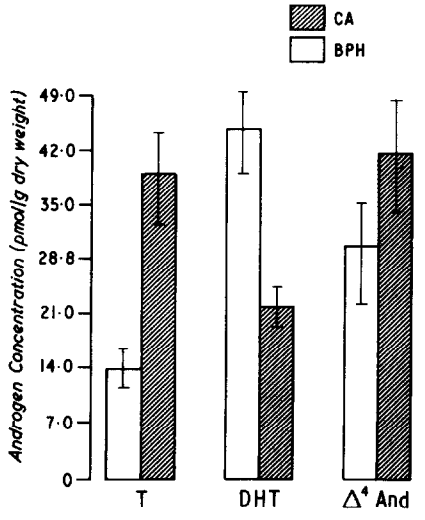


Fig. 1. Concentration of testosterone (T), dihydrotestosterone (DHT) and androstenedione ($\Delta^4$ And) in benign prostatic hypertrophy (open bars) and carcinomatous (hatched bars) tissues. Vertical lines indicate ± S.E.M. (From Habib *et al.*, 1976).

for the accumulation of testosterone in the malignant tissue remains, however, totally unexplained.

Recent work on rats and other experimental animals suggest that the zinc content of the prostate and the endocrine function of the gland are inter-related. Thus the administration of oestrogen to the male rat and castration decrease prostatic zinc levels whereas the administration of testosterone to the intact male increases the concentration of the trace metal in the gland [21, 22]. Since zinc levels are depleted in carcinoma of the prostate there may be a relationship between zinc and the abnormal testosterone levels. Habib *et al.*[6] studied the behaviour of prostatic zinc in the human pathological prostate. They reported a marked reduction in the concentration of the dihydrotestosterone when the endogenous zinc levels were below 3.0 μg/g dry weight; this apparently precedes the accumulation of testosterone which was observed in the malignant gland. In all cases the hormonal changes were usually manifested after the zinc concentrations had reached physiologically subnormal levels.

The formation of metal complexes of steroid sex hormones is well established [23]. The presence of these compounds in the prostatic tissue could probably influence the abnormal steroid dynamics of the pathological gland. However, attempts to locate these mysterious metal-androgen compounds were without much success [24].

B. *Enzyme activity*. The association of zinc with a number of metallo-enzymes including acid phosphatase, carbonic anhydrase and alcohol dehydrogenase is well established [25]. The activity of these enzymes depends on the presence of the trace metal [26]. In a recent paper [27], Rosoff and Spencer suggested that the cellular derangement resulting in neoplasia may indeed be linked with changes in the metal concentration of the enzymes. These metallo-enzymes, however, account for only a small fraction of the total zinc in the prostate [28] and the function of the bulk of the metal still, therefore, remains obscure.

The metabolism of testosterone to DHT in the androgen responsive tissue is catalyzed by the widely occurring enzyme, 5α-reductase [17, 29]. There are, of course, in the prostate gland a number of other enzymes besides the 5α-reductase which may metabolize natural androgens through one or more stages to DHT [30]. Available evidence suggests that one of the functions of zinc is to control this androgen metabolism at the cellular level. Support for such a hypothesis comes from the fact that the 5α-reductase activity can be completely inhibited by zinc at a concentration of $10^{-4}$ M and greater [31] whereas lower concentrations of $Zn^{2+}$ stimulated the reduction of testosterone to 5α-dihydrotestosterone by 20–30% of the control values [32].

The presence of a small amount of zinc is, however, required to maintain the normal cellular function of the prostate. It has become apparent from our own *in vitro* studies (Fig. 2) that the suppression of the reductase activity was also evident at zinc concentrations lower than $10^{-8}$ M. Since zinc levels in the neoplastic tissue are unusually low, this fall in enzymatic activity might account for the accumulation of testosterone in the malignant tissue.

Zinc can also influence the further metabolism of DHT. Although no studies have so far been carried out on the human prostate, Mawhinney and Belis[33] have shown that zinc can inhibit the formation of 5α-androstane,3α,17β diol in the rat ventral prostate and DHT levels accumulate consequentially. In view of the reported increase in zinc concentration of certain regions of the hyperplastic gland [7], it is surprising that the 3α- and 3β-hydroxysteroid dehydrogenase of the human prostate has not been more extensively investigated. It is possible that a decrease in the activity of these enzymes as a result of the increase in zinc levels may account for the accumulation of DHT in hyperplasia.

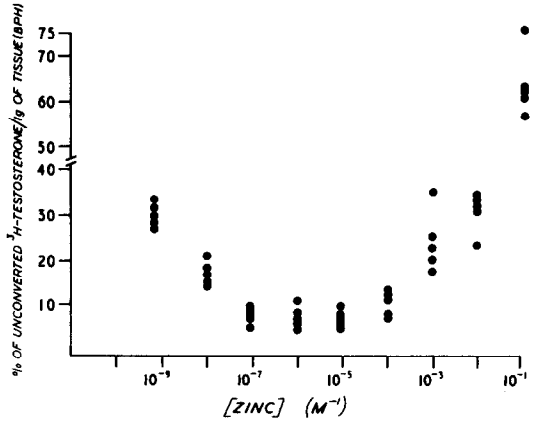


Fig. 2. The effect of divalent zinc ions on the reduction of testosterone in the prostatic tissue of five patients with benign prostatic hypertrophy.

C. *Androgen binding proteins.* Little is known of the chemical forms in which the high concentrations of zinc exist. More recently it has become apparent that zinc is closely linked with a histidine-rich protein [34] isolated from the cytosol fraction of the human prostate [35]. These cytosol proteins were further identified by polyacrylamide gel electrophoresis and the presence of a zinc binding component with a high affinity for testosterone and dihydrotestosterone was revealed [36]. This component is distinctly separate from any of the blood globulins and is particularly evident in the hypertrophied prostate [37]. It is, however, not yet known whether the mode of action of zinc on the androgen binding proteins is merely confined to the prostatic tissue or is, perhaps, associated with the more vital function of spermatogenesis. Noteworthy are the findings of significant amounts of metal binding protein fractions in the prostatic secretions of rats and dogs [38, 39]. We have, however, no evidence to suggest that these fractions are similar in composition to the metal binding proteins found in the prostatic tissue.

D. *Cadmium competition.* In view of the recent reports on the high incidence of carcinoma of the prostate amongst industrial workers exposed to high levels of cadmium [40, 41] a number of studies have been conducted on the toxic effects of cadmium in the prostate. Reed and Stitch[35] have shown that *in vitro* the metal competes with zinc and the uptake of radioactive zinc by minced prostatic tissue was drastically reduced in the presence of cadmium.

Furthermore, trace metal studies on the pathological gland revealed unusually high concentrations of cadmium in the malignant tissue [6]. Since cadmium shows a greater affinity for sulphur or nitrogenous ligand groups than zinc in the formation of their protein complexes [42], the displacement of zinc from the protein binding sites of the denaturized neoplastic prostate cells is, therefore, not totally unexpected.

More surprising, however, are our own recent observations on the rapid rise in the endogenous zinc concentrations of the hyperplastic tissue following an increase in the cadmium content (Fig. 3). Although these results are in disagreement with the earlier prostatic studies this phenomenon has already been observed in various tissues of different species [43]. Its occurrence is attributed by the authors to the ability of zinc to offset cadmium toxicity; this is probably achieved by the transport of large reserves of zinc from other parts of the body to the prostate.

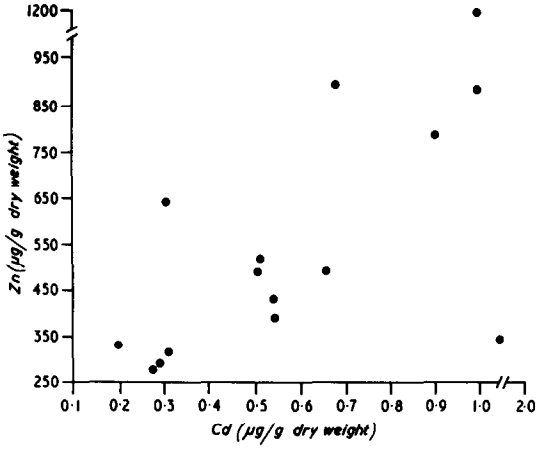


Fig. 3. Relationship between the concentration of zinc (Zn) and that of the cadmium (Cd) in prostatic tissue from the patients with benign prostatic hypertrophy. The Zn and Cd content of the tissue was determined by atomic absorption spectroscopy.

*Clinical application of zinc in prostatic cancer*

A. *Diagnostic tests.* There is a great need for the development of sensitive methods which can detect localized carcinomas. The reduced capacity of the malignant tissue to bind zinc was considered as a possible means for the application of radioisotope scintiscans in the study of prostatic diseases. However, in view of the difficulties experienced by many workers in the usage of radiozinc [44, 45] the usefulness of scintiscans as a diagnostic procedure remains of limited importance.

A number of investigations have also been carried out to correlate total plasma zinc concentrations with the pathological state of the gland. Present evidence suggests that these studies are not helpful in the diagnosis of the malignancy [46]. Attempts are, therefore, being pursued to identify a specific zinc transport protein in the blood which might correlate more closely with the glandular zinc concentration [47].

B. *Treatment.* Although Lo *et al.*[15] have suggested that dithizone might be useful in treating carcinoma of the prostate, more recent work has demonstrated no objective benefits from using this strong zinc chelating agent [9]. Indeed the further reduction of the already depleted zinc levels of the carcinomatous tissue might critically alter the hormonal balance of the gland and diminish its capacity to carry out the fundamental biochemical processes.

The possibility of using zinc for the treatment of prostatic cancer has, however, not been tested. The results showing the dependence of the androgen metabolism on the concentration of $Zn^{2+}$ suggest that zinc treatment might be useful for the control of neoplasia.

## CONCLUSION

The effects of zinc in prostatic tissue are not limited to a single biochemical parameter but might affect several pathways. These are particularly noticeable in carcinoma where the zinc concentration is at its lowest and the absence of the metal from the cytoplasm impedes the normal hormonal metabolism and reduces the enzymatic activity. The mechanism by which zinc modulates these specific functions, is, as of yet, unknown.

Of more interest, however, are the changes in the prostatic concentrations of zinc and androgens. These follow consistent patterns during the transition from

benign hypertrophy to malignant. Preliminary investigations have already revealed that these biochemical changes may indeed precede the histological transformation [48]; clinicians should consider, therefore, the possibility of using these biochemical changes as a support for information derived from histological examination.

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