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Zinc and Cadmium Concentration in Prostatic Carcinoma of Different Histological Grading in Comparison to Normal Prostate Tissue and Adenofibromyomatosis (BPH)

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Summary. Zn and Cd concentrations in tissue of normal prostate gland, BPH and prostatic carcinoma of different histological grades have been determined by atomic absorption spectrometry before therapy. We found a distinct biological antagonistic effect between Zn and Cd in the human prostate gland. We have seen an increasing amount of Zn in BPH, but a decrease in prostatic cancer. In contrast, we found a continuous increase of cadmium concentration from the normal prostate via BPH through carcinoma.

Key words. Prostatic carcinoma, Zinc and cadmium concentration.

Introduction

Since the investigations of Bertrand and Vladesco [2] in the 1920s, the abnormal high Zn concentration in the prostate gland and its secretion is known. Authors in later years [12] found a great individual difference of Zn-concentration in normal prostate glands. A very heterogeneous distribution was found, which does not parallel the anatomical structure of the prostate.

In the cytoplasma of the prostate gland other investigators found a Zn binding protein [20]. The accumulation and secretion of Zn, like all the specific functions of the prostate, are dependent on androgen influence [19, 22, 25] and begin at puberty. However, the mechanism for concentration Zn in the prostate [21] and its biological function are as yet unknown [23].

It is known that pathological processes in the prostate gland, e.g. prostato-vesiculitis and cancer, reduce the Zn accumulation in the prostatic tissue as well as in prostatic secretions [12, 6, 3]. Zinc is very important for the structural integrity of prostatic epithelium [10, 25]. The ability of Zn to influence the stability of RNA and DNA in other organs (in men) is also known. Some investigators [13] found a positive correlation between the influence of prolactin and Zn accumulation in the prostate. In this connection the evidence of Zn and testosterone-binding protein in the prostate adenoma [20] must be seen, because the specifity is not so certain here [9].

Because of the current uncertainty about the test treatment and the prognosis in prostatic cancer of different histological grades, we were interested to investigate the correlation between tissue concentrations of Zn and Cd in varying histological differentiation.

Material and Methods

Cadmium and zinc were determined by flameless atomic absorption spectrometry. A Jarrell-Ash double-beam spectrometer with a graphite furnace atomiser (Beckman Instruments) was used. The wet prostatic samples were weighed. The samples were heated at 180 °C until a constant weight was obtained.

The dried samples were dissolved in nitric acid (Suprapur, Merck) by slowly heating.

The atomic absorption measurements were realised by using 10 μl of the sample solution with a content up to 200 μg of dried tissue. The standard addition technique was used.

All results were related to dried samples of tissue, because the different content of liquid compounds in the wet samples gave very different analytical results.

We analysed two different kinds of prostatic tissues, taped samples and BPH. In the case of BPH and tissue of normal patients it was possible to investigate different samples of one prostate. There were large differences (up to 100%) in the concentration of cadmium and zinc within the prostate. The relative standard deviation of one sample by atomic absorption measurements was lower than 10%.

Results

Zinc Investigation

The Zn investigations were made on 16 normal prostate glands, 24 adenomas and 36 carcinomas of different histological grades before hormonal therapy.

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Table 1. Zn and Cd content of prostatic tissues of different histological grades.

Histology	Number of men	Zn concentration [µg/g] dried sample	Number of men	Cd concentration [µg/g] dried sample
Normal	16	348 ± 269	11	0.48 ± 0.24
Adenoma	24	774 ± 524	25	1.29 ± 0.93
Carcinoma	36	147 ± 103	33	1.62 ± 0.96
Adenocarcinoma	22	163 ± 81	19	1.81 ± 0.91
Solid carcinoma	8	109 ± 103	8	0.80 ± 0.47
Scirrhus carcinoma	6	79 ± 32	6	2.33 ± 0.76

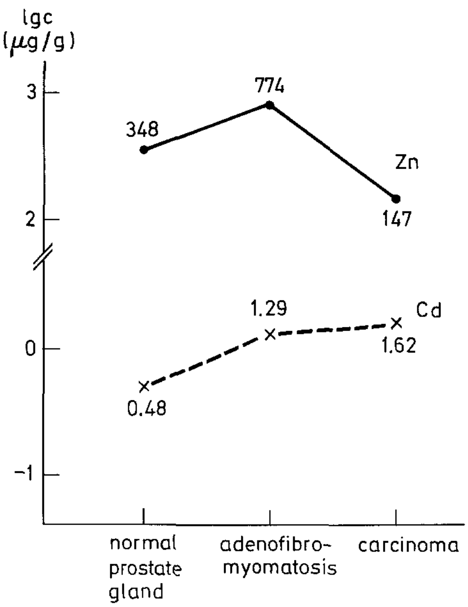

Fig. 1. Zn and Cd concentrations in prostatic tissues of different histology (µg/g of dried samples)

The normal prostatic tissues had an average content of 348 µg/g of dried sample. The tissues removed from patients between 12 and 44 years at autopsy after fatal accidents.

The Zn concentration in fresh adenomas of the prostate – mean age of the patients was 67 years – was 774 µg/g. The average amount in all 36 prostatic cancers was 147 µg/g (see Table 1).

We investigated the Zn concentration of prostatic carcinoma tissue with respect ot the histological grade.

The poorly differentiated scirrhus carcinoma with a bad clinical prognosis had the lowest level with 79 µg/g.

In the well differentiated adenocarcinoma we found a significant higher Zn-concentration (163 µg/g) compared to the solid carcinoma, which had a concentration of 109 µg/g (see Table 1).

Cadmium Investigation

Our Cd-studies were made on 11 normal prostate glands, 25 adenomas and 33 carcinomas of different histological grades.

In normal prostate tissue we found an average content of 0.48 micrograms Cd per gram of dried sample. These were from patients between 12 and 42 years at autopsy after fatal accidents.

The Cd-content in fresh adenomas of prostate of patients with a mean age of 71.6 years was 1.29 µg/g (occupational exposure during lifetime and other factors were unknown).

The average amount of all 33 prostatic cancers was 1.58 µg/g the highest Cd-Concentration in tissue.

Next we observed the Cd concentration of the prostate carcinomas with respect to their histological grade. The poorly differentiated solid carcinoma had the lowest level, 0.80 µg/g.

We found in well-differentiated adenocarcinoma a Cd-concentration of 1.81 µg/g. The highest level of cadmium was found in scirrhus carcinoma with 2.33 µg/g.

In Fig. 1 the contrast in the average amount of zinc and cadmium in the normal prostate gland, the adenoma of prostate and prostatic cancer is shown.

Discussion

Cadmium has been classified as a non essential trace element [14]. It is present in food. tobacco, air and water as a contaminant. The absorption of ingested cadmium is rather small, whereas that of inhaled Cd is greater. Smoking can be an important source of cadmium exposure. This amount is comparable to the daily gastrointestinal absorption from ingested food [24]. The absorbed Cd is excreted very slowly and it accumulates primarily in the liver, where it is bound to metallothionein, a special cadmium binding protein [18], in kidney and in other organs.

Among a number of studies associating Cd with chronic disease, few reports have been relating exposure to cadmium with the occurrence of malignant disease, particularly in the prostate [7, 8]. We were not able to find any investigations in normal prostate and prostatic cancer of different histological grades. Cadmium acts as a competitive inhibitor of zinc and Zn-binding proteins [8, 4, 5] and produces malignant tumours in animals. Partial or total inhibition of zinc-dependent enzymes, like carbonic anhydrase and others, is a possible mechanism for the carcinogenicity of the metal.

One of the consequences of the many similarities between Zn and Cd could be the direct exchange of Zn by Cd in zinc-containing enzymes, e.g. phosphatases, carboxypeptidases, carbonic anhydrase, which normally contain Zn bound to sulphur [18]. This could be a possible interpretation for our results in Zn and Cd determinations and the antagonistic effect of zinc and cadmium in the human prostate. But there is no general agreement on this point yet [18]. Cadmium has a great affinity for nitrogen, oxygen and sulphur groups. This metal has also a strong affinity for membranes, which contain phosphatidyl-serene or ethanolamine. In vitro experiments have shown that Cd induces the expansion of monolayers of these lipids. Membrane-bound enzymes will therefore be mostly influenced by changes in membranes and by changes in electric charge. Possible carcinogenicity of Cd in man has been reported from Britain [8] where deaths from carcinoma of prostate have been associated with cadmium exposure in industrial workers. Kjellström [16] observed a tendency for an increased mortality in prostatic cancer among Cd-Ni-battery factory workers. The way in which Cd might act as a carcinogen is much disputed.

In a recent experimental study Aughy et al. [1] showed that prostate cells are capable of retaining Cd in measurable amounts up to 6 weeks after injection, but that areas with high Zn concentration retain less Cd then areas with low zinc. They also found histological changes suggestive of carcinogenic activity by Cd. In experiments the carcinogenic action of cadmium could be prevented by injection with Zn salts [16]. It also has been demonstrated in several animal experiments that selenium has an antagonistic effect on heavy metals like Cd [14, 15]. Cadmium does change metabolism, but whether these changes are primary or secondary effects is difficult to say [18].

Some aspects of the role of Cd in carcinogenesis were also compiled in a rewiev by Piscator [17].

In this preliminary study we found a distinct biological antagonistic effect between Zn and Cd in the human prostatic gland. It is possible that the habits of the individuals take a leading part in accumulation of Cd. The influence of oral intake of Zn and Cd and of environmental exposure as well as the possible role of industrial exposure could all be important. Most of our patients were rural residents. There were also no significant differences in tobacco consumption between our cancer patients and the BPH group.

The way in which changes of Cd and Zn metabolism might influence carcinogenesis, especially in carcinoma of the prostate, will be reserved for further investigations. We intend to examine the relation of Zn and Cd content in fractions of prostatic cells.

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