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Clinical and Epidemiological Features of Dishormonal Diseases and Breast Cancer in Men in the Aral Sea Region

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Abstract A significant number of scientific papers have been devoted to breast cancer in the female population, while insufficient attention has been paid to cancer and dyshormonal diseases of the mammary glands in men. Nevertheless, this issue is becoming more urgent every year. Although breast cancer in men is a relatively rare disease (1-2% of the number of these tumors in women), it is not inferior to “female” cancer in terms of malignancy, and sometimes even surpasses it. Changes in the mammary gland in men are primarily associated with hormonal imbalance, the manifestation of which is gynecomastia. Until now, there is no consensus on the relationship between gynecomastia and breast cancer, although it has been established that the incidence of malignant tumors against the background of gynecomastia makes up 3.9 - 40.0% of cases.

Keywords Breast cancer, Gynecomastia, Oncoepidemiology, Hormone therapy

1. Introduction

The issue of precancerous diseases and breast cancer is very relevant today not only in Uzbekistan but throughout the world. The increased interest to breast cancer, first of all, is associated with the increasing number of diseases observed in recent years in the world [1-4].

On average, male breast cancer occupies a leading position in the structure of the incidence of malignant neoplasm of this organ in both sexes [5-8]. Breast cancer averages 0.2% in the structure of the incidence of men with MN. On average, about 26 males die from breast cancer in Uzbekistan, accounting for 1.3% of all patients who died from breast cancer and 0.18% of all men who died from MN.

Until now, there is no consensus on the relationship between gynecomastia and breast cancer, although it has been established that the incidence of malignant tumors against the background of gynecomastia makes up 3.9 - 40.0% of cases.

Men, as well as women, have a genetically determined predisposition to the development of breast cancer. More than 40% of breast cancer cases in men are hereditary [9-11]. Breast cancer genes BRCA-1 and BRCA -2 were studied in more than 21 families. Mutations in BRCA – 2 have been identified in men with breast cancer [12]. The complexity of diagnosis is aggravated by the fact that male breast cancer has to be differentiated from a large group of this organdiseases, united by the common name "gynecomastia". Statistical data on the frequency of gynecomastia are few and contradictory and occur between the ages of 17 and 80 years [14-18]. Breast cancer in men can be developed both against the background of gynecomastia and without it. Proof of gynecomastia transformation into cancer can only be the detection of pre-invasive cancer in the duct epithelium.

Currently, the uneven spread of malignant neoplasms in various territories is largely due to the influence of carcinogenic and modifying environmental factors, such as anthropogenic pollution, occupational hazards, as well as a number of climatic and geographical features. Geochemical factors (both natural and techno genic) are among the important components of the external environment, which cannot but influence the development of cancer-epidemiological processes. According to a number of authors, the leading role in oncogenesis is played by seven bioelements, which include copper, manganese, zinc, cobalt, iron, 7 molybdenum, iodine [19-22]. The influence of these elements on the growth of malignant neoplasms in the gastrointestinal tract, maxillofacial region, hormone-dependent organs, including the mammary gland, has been determined.

Analysis of the incidence rates of dyshormonal diseases and breast cancer in men in the Aral Sea region revealed their growth. Studies carried out in this region have shown that the spread of malignant tumors of the female mammary gland in different landscape zones is heterogeneous and this is due to the uneven distribution of individual microelements in the soil and in water sources. Taking into account the heterogeneity of the biogeochemical structure of the Aral Sea region and also the increase in the incidence of

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gynecomastia and breast cancer among the male population, it should be noted that the study of this pathology spread features and the identification of factors contributing to its development is relevant not only in terms of expanding knowledge on the occurrence of this pathology, but also provides new materials for scientifically based measures of anticancer control.

Aim of the study was to study the peculiarities of the spread of the mammary glands diseases in men living in various landscape zones of the Aral Sea region and to determine the relationship between the indicators of morbidity, the trace element composition of the blood, the level of sex hormones.

2. Material and Methods

In order to determine the reaction of the male body to the geochemical composition of the environment, we examined 342 men with dyshormonal hyperplasia and breast cancer at the age from 12 to 80 years and older: 130 cases— with diffuse gynecomastia, 114 — with nodulargynecomastia, 76 — with mixedgynecomastia, 15 — with breast cancer and 7 people with other pathologies. The diagnosis was determined on the basis of objective data, additional examination methods, which included X-ray and ultrasound mammography and mandatory cytomorphological verification.

The groups were formed with maximum homogeneity. The studied clinical groups consisted of the indigenous newcomer population living in the Aral Sea region for at least 10 years. The majority of the surveyed were represented by 135 workers (39.5+2.6%), employees and intellectuals - 75 (21.9+2.2%), schoolchildren and students - 58 (16.9+2.0%), collective farmers - 43 (12.6+1.8%), entrepreneurs - 13 (3.8+1.0%), unemployed - 18 (5.3+1.2%). We did not find the reliability of the difference in the zonal distribution of the professional factor. Consequently, the professional employment of men is evenly represented in the northern, transitional and southern zones. The control group included 50 men of the corresponding age groups, living in the Aral Sea region for at least 20-30 years, professionally employed and who, after a preventive examination, were found to be practically healthy. The food ration of the indigenous newcomer population in the Aral Sea region in all clinical groups mainly consisted of locally produced products.

Taking into account the objective of the study and the accepted division of the entire territory of the Aral Sea region, depending on the soil structure into zones (northern, transitional, southern), the role and place of the environment in the diagnosis and assessment of the main parameters of homeostasis in men with dishormonal diseases and breast cancer were determined as factors of increased cancer risk. The incidence of breast cancer in the districts was studied using the registration form 030-6 / U for the period 2010-2020.

Determination of trace element analysis of patients' blood with dyshormonal diseases of the mammary glands and breast cancer was carried out by atomic absorption spectrophotometry. Determination of the hormonal profile of peripheral blood was carried out on the basis of the laboratory of radioisotope diagnostic methods. 295 samples were analyzed. Determination of folicle-stimulating hormone (FSH), luteinizing hormone (LH) was carried out by radioimmunoassay (RIA). Prolactin and testosterone were determined using CIS International kits. In parallel, the hormone determination of FSH, LH, prolactin, testosterone, estradiol was carried out by the method of enzyme-linked immunosorbent assay (ELISA).

X-ray examination of the mammary glands (mammography) was performed using a mammographic X-ray apparatus mammo DIAGNOST UG manufactured by PHILIPS. Ultrasound examination was carried out on Fukuda Denshi 5000 and SonoAce 4800 HD devices using a 7.5 linear transducer; 10 MHz. We performed puncture of the mammary glands according to the generally accepted technique with a thin needle 6-10 cm long and 1 mm in diameter. The puncture site was determined on the basis of clinical, sonographic and radiological data. From the punctate and secretions from the nipples of the mammary glands, preparations were made - smears, which were subsequently stained using the Pappenheim method. The removed breast tissue was fixed in 10% neutral formalin and embedded in paraffin using a standard technique. The prepared paraffin sections with a thickness of 5 μm were stained with hematoxylin and eosin. The hormonal profile of peripheral blood was determined by RIA and ELISA.

The immunological basis of the in vitro radio test (RIA) reaction is similar to the reactions occurring in the human immune system "antigen - antibody".

The hormonal profile ELISA technique is based on the principle of a two-site (sandwich) test system.

The elemental composition of blood samples was determined using a Hitachi atomic absorption spectrophotometer (Japan). Taking into account the possibility of daily fluctuations in the amount of mineral elements in the blood, it was taken in the morning until 10 o'clock on an empty stomach from a vein on an outpatient basis. The technique of the atomic absorption method for the determination of elements consisted in the decomposition of the analyzed sample, spraying the resulting 41 solution in an air-acetylene flame or in a flame of a mixture of nitrous oxide and acetylene, depending on the element to be determined, measuring the value of atomic absorption of resonance radiation by neutral atoms of the determined elements formed during the atomization of the sample.

Calculations were performed according to the third category of accuracy, for which its margin is measured by the formula: 1 <Z.

3. Results

As a result of studies by atomic absorption spectrophotometry, the maximum amount of the trace element zinc (559.8 + 39.1 μg / g) and manganese (5.54 + 0.06 μg / g) was found in the peripheral blood of patients with diffuse gynecomastia. They also had the minimum content of cobalt (9.88 + 0.39 μg / g) and copper (63.17 + 3.16 μg / g) (Tab. 1).

The reliability of the difference in the zinc content between the control group was determined as the minimum t = 0.5, and manganese t = 3.1 as the highest. In patients with a nodular variant of gynecomastia, we noted the opposite regularity. The maximum in their content were trace elements of cobalt (20.98 + 0.84 mcg/g, t = 17.3), copper (79.54 + 3.98 mcg/g, t = 3.0), strontium (15.90 + 0.79 mcg/g, t = 6.6), lead (47.20 + 15.10 mcg/g, t = 1.3) and cadmium (25.20 + 6.05 mcg/g, t = 2.1). In men with a mixed form of dyshormonal hyperplasia, the indicators of the trace element background occupied an average position between the values of trace elements in men with other forms of gynecomastia (diffuse and nodular).However, we noted an equal content of manganese indicators in men with nodular and mixed forms of gynecomastia (5.49 + 0.05 mcg/g, t = 0.5). Investigations conducted to study the content of trace elements zinc, manganese, cobalt, copper in men with dyshormonal hyperplasia of the mammary glands allow us to state the following: there is a statistically significant decrease in the content of tumor growth inhibitors - zinc (t = 3.3, p). The results of the study of the mineral profile by ICP - MS method of peripheral blood of men with mammary galnds pathology are presented in Table 2.

Table 1. The content of zinc, manganese, cobalt, copper, strontium, lead and cadmium in the peripheral blood of men with dyshormonal hyperplasia, μg / g

Trace element	Control group n=30	Patients with diffuse gynecomastia n=20	Patients with nodular gynecomastia n=20	Patients with mixed gynecomastia
Zinc	532.21±37.25	559.80±39.10	382.90±26.80	458,80±32,10
Difference reliability, t	-	0.5	3.3	1.5
Manganese	5.30±0.05	5.54±0.06	5.49±0.05	5.49±0.05
Difference reliability, t	-	3.1	2.7	2.7
Cobalt	8.07±0.32	9.88±0.39	20.98±0.84	19.15±0.77
Difference reliability, t	-	3.6	17.3	13.3
Cooper	64.32±3.22	63.17±3.16	79.54±3.98	67.01±3.35
Difference reliability, t	-	0.3	3.3	0.6
Strontium	9.76±0.49	13.50±0.68	15.90±0.79	11.59±0.58
Difference reliability, t	-	4.5	6.6	2.4
Lead	25.16±8.04	17.20±5.50	47.20±15.10	33.44±10.69
Difference reliability, t	-	1.4	1.3	0.6
Cadmium	10.99±2.64	15.21±3.65	25.2±6.1	18.90±4.54
Difference reliability, t	-	0.9	2.1	1.5

Table 2. The content of zinc, manganese, cobalt, copper, strontium, lead and cadmium in the peripheral blood of men with breast cancer in men, μg / g

Trace element	Patients with diffuse gynecomastia n=20	Patients with nodular gynecomastia n=20	Patients with mixed gynecomastia	Breast cancer patients n=15	Control group n=20
Zinc	5.07±0.05	5.25±0.05	4.56±0.05	5.64±0.06	6.12±0.06
Difference reliability, t	13.5	11.2	20.0	6.0	-
Manganese	33.92±0.34	48.28±0.49	16.13±0.16	18.89±0.19	22.15±0.22
Difference reliability, t	29.4	48.7	22.3	11.2	-
Cobalt	0.57±0.01	0.73±0.01	1.62±0.02	2.51±0.03	0.79±0.01
Difference reliability, t	15.7	4.28	37.7	55.5	-
Cooper	0.72±0.01	0.65±0.01	0.61±0.01	0.67±0.01	0.55±0.01
Difference reliability, t	12.1	7.14	4.3	8.6	-
Strontium	34,27±0,34	39,35±39	16.26±0.16	23.81±0.24	21.29±0.21
Difference reliability, t	32.5	40.9	18.9	8.4	-
Lead	66.89±0.67	51.14±0.51	18.66±0.17	42.60±0.43	17.86±0.18
Difference reliability, t	71.1	66.6	3.2	53.1	-
Cadmium	0.82±0.01	0.96±0.01	0.38±0.01	0.71±0.01	0.74±0.01
Difference reliability, t	5.7	15.7	25.7	2.1	-

When studying inhibitors of tumor growth - zinc and manganese, we found the following regularities: the zinc content in the blood of the surveyed had tendencies of a uniform - sequential increase of indicators from the group of patients with the nodal form of gynecomastia (4.56 + 0.05 μg / g, t = 20.0), then the group with diffuse gynecomastia (5.07 + 0.05 μg / g, t = 13.5) and mixed gynecomastia (5.25 + 0.05 μg / g, t = 11.2). We found the maximum level of zinc in the blood of men with breast cancer (5.64 + 0.06 μg / g, t = 6.0). In all patients the zinc content in the peripheral blood wa less than in the control group (6.12 + 0.06 μg / g).The manganese content in the blood of those examined with breast pathology ranged from 16.13 + 0.16 ng / g in patients with nodular dyshormonal hyperplasia of the mammary glands to 48.28 + 0.49 ng / g in men with mixed gynecomastia. A high content of manganese was also noted in the blood of patients with diffuse gynecomastia - 33.92 + 0.34 ng / g. In men with breast cancer, the manganese content was 18.89 + 0.19 ng / g. A high content of manganese was revealed in patients with diffuse and mixed forms of gynecomastia (t = 29.4; 48.7, respectively). These indicators were higher not only in the group with nodular gynecomastia, but also in the control group and the group of men with breast cancer. The maximum content of cobalt as a result of our studies was noted in men with a malignant process in the mammary glands (2.51 + 0.03 ng / g, t = 55.5) and with nodulation of a dyshormonal nature (1.62 + 0.02 ng / g, t = 37.7). A similar trend was recorded for cadmium. The maximum indicators were recorded in groups with diffuse nodular hyperplasia of the mammary glands (0.96 + 0.01 IU / t, t = 15.7), with diffuse gynecomastia - 0.82 + 0.01 ng / g (t = 5, 7) and with breast cancer (0.71 + 0.01 ng / g, t = 2.1).

Thus, studies of the microelement profile, carried out by atomic absorption spectrophotometry and ICP-MS in the peripheral blood of men with mammary glands pathology allowed us to reveal the regularities of the content of zinc and manganese as inhibitors of tumor growth: equally high rates in patients with diffuse and mixed forms of gynecomastia, equally low in men with nodular form of dyshormonal hyperplasia. Equally increased levels of cobalt and copper were found in patients with nodular gynecomastia by atomic absorption spectrophotometry. The ICP - MS method revealed the highest cobalt content in patients with breast cancer.

Both qualitative and quantitative disorders in hormone formation were observedat gynecomastia: the trend of increasing the level of LH - 0.7 + 0.1 mMU / ml, 4.7 + 0.4 ng/ml and prolactin - 48.8 + 9.3 ng/ml, 13.7 + 2.6 mIU / ml, violation of the ratio of sex hormones towards the predominance of female sex hormones and an increase in the level of FSH - 1.1 + 0.1 IU / L, 5.7 + 0.6 mIU / ml (Tab. 3).

In breast cancer dysfunctions of the pituitary gland combined with dysfunction of the gonads were also recorded, but FSH indicators were 1.2 ± 0.1 IU / L, 5.9 ± 0.6 mIU / ml and LH - 0.7 ± 0, 1 mMU / ml, 4.7 ± 0.4 mIU / ml did not differ significantly from those in gynecomastia. The prolactin content (48.0 ± 9.1 ng / ml; 13.5 ± 2.6 mIU / ml) in patients with breast cancer, although was increased in comparison with the control group, but was at the same level with the indicators in gynecomastia (48.8 ± 9.3 ng/ ml; 13.7 ± 2.6 mIU / ml). The concentration of testosterone in the blood of men with breast cancer (21.5 ± 2.7 nmol / L; 19.1 ± 2.4 ng / ml) was almost 1.4 times higher than in patients with dyshormonal hyperplasia (15.8 ± 1.98 nmol / L; 14.06 ± 1.77 ng / ml) and 17.4% higher than in the control group. Patients with gynecomastia 67 had a minimum testosterone content (15.8 ± 2.0 nmol / l; 14.1 + 1.8 ng / ml).The content of estradiol in breast cancer tended to decrease (21.6 ± 5.4 pg / ml) compared with the group of men with dyshormonal hyperplasia (51.3 ± 12.8 pg / ml), although it was higher than the control group (17 , 2 ± 4.3 pg / ml) (Tab. 4).

Table 3. FSH, LH, prolactin, testosterone and estradiol levels in men with gynecomastia

Hormone	**Control group**	**Gynecomastia patients**	**P**
	N30	**N195**	
FSH, IU / L	0.8±0.1	1.1±0.1	<0.01
LH,mMU / ml	0.6±0.1	0.7±0.1	>0.01
Prolactin, ng/ml	25.6±4.9	48.8±9.3	<0.05
Testosterone, Nmol / L	18.3±2.3	15.8±2.0	>0.05
	B20	N40	
FSH, IU / L	4.3±0.5	5.7±0.61	<0.01
LH, mMU / ml	4.1±0.3	4.7±0.32	>0.01
Prolactin, ng/ml	7.2±1.4	13.7±2.61	<0.05
Testosterone, Nmol / L	16.3±2.1	14.1±1.77	>0.05
Estradiol, pg / ml	17.2±4.3	51.3±12.82	>0.05

Table 4. FSH, LH, prolactin, testosterone and estradiol levels in men with breast cancer

Hormone	**Control group**	**Breast cancer patients**	**P**
	N30	**N10**	
FSH, IU / L	0.8±0.1	1.2±0.1	<0.01
LH,mMU / ml	0.6±0.1	0.7±0.1	>0.01
Prolactin, ng/ml	25.6±4.9	48.0±9.1	<0.05
Testosterone, Nmol / L	18.3±2.3	21.5±2.7	>0.05
	B20	**N10**	
FSH, IU / L	4.3±0.5	5.9±0.6	<0.01
LH, mMU / ml	4.1±0.3	4.7±0.4	>0.01
Prolactin, ng/ml	7.2±1.4	13.5±2.5	<0.05
Testosterone, Nmol / L	16.3±2.1	19.1±2.4	>0.05
Estradiol, pg / ml	17.2±4.3	21.6±5.4	>0.05

4. Discussion

Thus, it is possible to assume that the changes found by us in the content of trace elements zinc, manganese, cobalt, copper, strontium, lead and cadmium in the blood of the examined men can lead to dysfunction of the pituitary gland and be accompanied by changes in the secretion of FSH, LH, prolactin, testosterone and estradiol. This imbalance, in turn, determines the morphological and functional state of the mammary glands, its clinical manifestations and, possibly, acts as a factor predisposing to the development of dyshormonal hyperplasia and breast cancer in men.

Comparison of the primary morbidity with the geochemical situation in three zones of the Aral Sea region revealed the following pattern: an increase in the content of copper and cobalt occurs in parallel with an increase in the incidence of gynecomastia and breast cancer in the direction from north to south. The concentration of zinc and manganese decreases in the same direction. Besides, in the transitional and southern provinces of the Aral Sea region an increased content of toxic elements (strontium, lead, cadmium) has been noted. This confirmed the relationship between the primary incidence of gynecomastia and malignant tumors of the mammary glands in men with a trace element composition of soils, water sources and food. The average values of the levels of copper, zinc, manganese and cobalt in soils, surface waters and food products were used.

The coefficient of canonical analysis reflects the general relationship between the incidence of breast cancer in men and the microelement background of the biosphere. Thus, a significant dependence of the incidence rate was determined with a high level of cobalt content ($K = 2.822 + 0.780$, p). Against the background of the unfolding imbalance of hormones in men with dyshormonal diseases of the mammary glands, the activity of male sex hormones increases, which, apparently, indicates the work of compensatory mechanisms that require the involvement of the trace element zinc ($R = 0.178 + 0.015$) involving in the production of testosterone. In conditions of increased lead content in the transitional and southern zones of the Aral Sea region, a high correlation coefficient was noted between lead and the studied hormonal complex in patients with gynecomastia ($R = 0.263 + 0.220$).

The relationship between each of the studied bioelements and indicators of the hormonal profile in the peripheral blood of men with breast cancer was traced. The accumulation of zinc and manganese in the tissue of patients with breast cancer is apparently a protective reaction, since during the development of the tumor process we noted a decrease in the content of these biometals in the peripheral blood. It creates conditions for hyperestrogenemia (21.6 + 5.4 pg / ml), and as a consequence, an increase in proliferative processes in the mammary glands.

When studying the content of cobalt, copper, lead, strontium and cadmium in peripheral blood and in mammary glands tissue, their promoter activity was found, possibly leading to the development of breast cancer in men, while zinc and manganese act as inhibitors. However, it would be wrong, in our opinion, to approach the issue of the correlation between the microelement composition of the biosphere and the incidence of breast cancer purely mechanically, without taking into account the interaction of bio elements with each other and with a group of toxic microelements 98 (strontium, lead and cadmium). Excessive intake of cadmium and lead in the human body leads to a deficiency in zinc intake. The transitional and southern biogeochemical zones are already deficient in the content of trace elements zinc and manganese in mobile forms, and the layering increased content of trace elements strontium, lead and cadmium further aggravates this condition, increases the incidence of nodular gynecomastia and breast cancer among the male population.

5. Conclusions

Thus, the revealed features of hormonal and mineral homeostasis disorders in men are closely related to the features of the microelement composition of the environment. They, in turn, have an impact on the different incidence of dyshormonal hyperplasia and breast cancer in the Aral Sea region. Therefore, for the formation of groups of increased risk for the development of dyshormonal diseases and breast cancer in men of the Aral Sea region, along with genetic and modifying factors, it is necessary to take into account the microelement composition of the environment.

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