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Research Article

Zinc metabolism in healthy men and in patients with chronic bacterial prostatitis

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Abstract

Introduction: Zinc is a vital trace element, which regulates metabolism of a prostate gland. It has been established that a low plasma zinc level in men increases the risk of chronic prostatitis and vice versa, chronic prostatitis is often accompanied by zinc deficiency in the prostate gland. The purpose of this study is to research the features and possible correlations of zinc metabolism disorders at systemic (in blood) and local (in prostatic fluid) levels in healthy men and patients with chronic bacterial prostatitis (CBP).

Materials and methods: Ninety patients with CBP (main group) and thirty healthy men (control group) were randomized by age (mean age 38.5±2.9 years) and examined. In addition to standard examinations, the zinc levels in blood serum and prostatic fluid were determined, and the oxidative status of the prostate gland was assessed (the level of reactive oxygen species (ROS), conjugated dienes, malondialdehyde, superoxide dismutase (SOD) activity in the prostatic fluid) according to standard methods.

Results and discussion: In patients with CBP, the absolute deficiency of plasma and prostatic zinc was detected 2.89 and 2.5 times more often, respectively, than in healthy men ($p < 0.05$). At the same time, both the patients with CBP and healthy men had significant correlations between plasma zinc and zinc in prostatic fluid ($r = 0.345$; $n = 37$; $p = 0.001$ and $r = 0.156$; $n = 30$; $p = 0.001$; respectively). A significant positive correlation between the zinc level and the activity of SOD in prostatic fluid was revealed only in the patients with CBP ($r = 0.389$; $n = 90$; $p = 0.001$).

Conclusion: Zinc concentration in blood plasma does not objectively reflect zinc metabolism disorders in the prostate gland, and therefore the determination of zinc in prostatic fluid is the most reliable and sensitive method for assessing zink disorders in patients with CBP.

Keywords

chronic bacterial prostatitis (CBP), oxidative stress, oxidative disorders, zinc, zinc deficiency, superoxide dismutase (SOD), correlation relationships

Introduction

Zinc is one of the key trace elements that ensures human body balance control throughout his/her life, while its total content in the body is quite small and averages 1.5–3.0 g (Steinbrenner and Klotz 2020). With age, the absorption of dietary zinc decreases significantly, so its deficiency can make an additional negative contribution to the pathogenesis of age–associated human diseases (Steinbrenner and Klotz 2020).

Zinc is extremely necessary for a huge number of catalytic, structural, and regulatory physiological processes. It is a part of or supports the activity of about 100 intracellular enzymes that catalyze the key stages of DNA and RNA synthesis. Zinc is involved in almost all stages of cell maturation, so it acts as a natural regulator of the cell division, differentiation, proliferation and apoptosis. In addition, zinc is able to stabilize cell membranes, as well as has an immunomodulatory effect on the T- and B-cells of the immune system (Liflyandskii 2010).

In a male body, the largest part of zinc is concentrated in the prostate gland, which is perhaps the most zinc–dependent organ. So, the zinc concentration in tissues of internal organs in men is 30 mcg/g, but the prostate gland contains 7 times more zinc (on average 209 mcg/g). In the blood plasma of men, the concentration of zinc is 1 mcg/g, while in the prostatic fluid it reaches 590 mcg/g. Therefore, zinc plays one of the key roles in ensuring normal physiology of the prostate gland (Borisov 2015). A significant part of zinc in prostate cells is part of the zinc–dependent superoxide dismutase (Zn–SOD), which catalyzes the dismutation reaction of the peroxide radical and is one of the three key specialized enzymes of the antioxidant defense system (ADS) of cells that resist oxidative stress; therefore zinc also acts as a natural antioxidant in the prostate gland (Rosa et al. 2021). In experimental studies, it was demonstrated that, on the one hand, in chronic bacterial prostatitis (CBP), prostate cells lose their ability to accumulate zinc, and, on the other hand, infection of the prostate gland is associated with a lower zinc concentration in the prostate fluid (Zhao et al. 2016; Bratchikov et al. 2020; Santos et al. 2020; Daragó et al. 2021), which makes possible the suggestion about the presence of a significant bilateral relationship between zinc deficiency in the prostate gland and the risk of CBP, which now has been confirmed at the level of thematic meta–analysis (Cui et al. 2015).In clinical practice, urologists use various dosage forms of zinc; however, this therapy is most often carried out ”in the dark”, i.e. empirically, without appropriate laboratory determination of the zinc level either in the blood or in the prostatic fluid. In the available literature, we have found no data on the diagnostic value and sensitivity of zinc determination in different internal environments, and the correlation between plasma and prostatic zinc levels in healthy men and in patients with CBP remains still unknown. This predetermined the purpose of the study, which, in connection with the above, seems relevant for practical urology.

Aim of the study: to study the features and possible correlation of systemic (in blood) and local (in prostatic fluid) zinc metabolism in healthy men and patients with chronic bacterial prostatitis (CBP).

Materials and methods

General description of groups

Ninety patients with CBP aged 24–46 years (mean age 38.2±1.4 years) (the main group) and 30 clinically healthy men aged 20–45 years (mean age 35.5±1.5 years) with excluded prostate pathology after the complex diagnosis (control group) were examined.

Study design – a concurrent prospective full-design randomized study

All men within the study were subjected to the same comprehensive examination, and the results of the control group were taken as the reference values of the conditional norm of the studied parameters. All patients who entered this study and completed it, as well as clinically healthy men of the control group, had beenwere previously informed about the goals and objectives of the study, and each had filled out an informed consent to participate in this study and for the obtained results to be used for scientific purposes.

Entry criteria:

- The clinical symptoms of CBP (the main clinical sign is chronic pelvic/prostatic pain with characteristic irradiation) in combination with relevant laboratory data (identification of significant pathogens in the prostatic fluid in a diagnostically significant titer $>10^3$ CFU/ml);
- The absence of a history of surgery or injuries of the pelvic region and perineum;
- Absence of symptoms of any neurological disease;
- Absence of type 1 or type 2 diabetes mellitus;
- Absence of anamnesis and clinical and laboratory signs of STIs at the time of the study;
- Men aged under 50.

Exclusion criteria:

- The clinical and sonographic signs of any infravesical obstruction;
- The lower urinary tract symptoms (LUTs) typical for an overactive bladder (OAB);
- Therapy of any type of LUTs or chronic pain less than 3 months ago, which did not bring positive results;
- Taking medications that can affect the bladder and/or prostate gland for less than 6 months before the start of the study;
- Existing or suspected prostate cancer (total blood PSA > 4 ng/ml).

From the men of the control group and patients with CBP of the main group, complaints and anamnesis were collected; among them, CPSI–QL questionnaires were conducted, and general, special urological, microbiological, laboratory, sonographic examinations were performed using standard methods. Various modifications of biochemical analysis of prostatic fluid were performed to assess the oxidative status of the prostate gland.To determine the level of reactive oxygen species (ROS) in the prostatic fluid, the method of luminol-dependent chemiluminescence (LDCL) was used, and the main indicators of this method were the light sum (LS) and the maximum amplitude of the glow (MaxG), which corresponded to the level

of formation of reactive oxygen species (ROS) (Faulkner and Fridovich 1993). To assess the adequacy of redox reactions in the prostatic fluid, the level of intermediate products (conjugated dienes, malone dialdehyde) of lipid peroxidation was determined and the activity of one of the key specialized universal enzymes of intracellular antioxidant defense system – superoxide dismutase (SOD) – was evaluated. Determination of conjugated dienes and malone dialdehyde was performed by the method of Stalnaya I.D. and Garishvili T.G. with spectrofluorimetry after reactions with thiobarbituric acid (Stalnaya and Garishvilli 1977). The activity of superoxide dismutase (SOD) of prostatic fluid was determined by spectrophotometry according to the technique of Mistra H.P. and Fridovich I. in the modification of Kostyuk VA et al. (1990), based on the determination of the degree of inhibition of the quercetin autooxidation due to the fact that one of the intermediate products of this reaction is a superoxide anion radical. Determination of the zinc concentration in blood plasma was performed by the colorimetric method (IFCC), based on the formation of a chelate of zinc with dithizone (Shachneva and Zukhayraeva 2015). The zinc concentration in the prostatic fluid was determined by the method of X–ray fluorescence analysis (XFA), based on the secondary X-ray irradiation of a sample, which occurs under the action of more intense X–rays, on a portable Russian analyzer of the MAK-6 series (St. Petersburg) (Bekman 2012).

Statistical data processing

Statistical processing of the study results was carried out using the STATISTICA 12.0 software (StatSoft, USA). To study the correlation of variables, the Spearman correlation coefficient (r) was determined. The r value was interpreted as follows: <0.25 – weak correlation; 0.26–0.75 – moderate correlation; >0.75 – strong correlation. To assess the intergroup differences in the values having a continuous distribution, the Student's t-test was used. The level of statistical significance of the difference between the indicators was at $p < 0.05$.

Results and discussion

The results of measurements of zinc levels in the blood (serum zinc) and prostatic fluid (prostatic zinc) showed that the men of the control and main groups had different trends in zinc levels in the studied biological fluids. Thus, in the control group, only in 3/30 (10.0%) men, the absolute serum zinc level was less than the lower limit of the general population reference (<543 mcg/L), reaching a minimum value of 489 mcg/L. In 4/30 (13.3%) men of the control group, the absolute serum zinc level was within the lower–middle tertile of the range of the average population reference values (543–738 mcg/L), and in the remaining 23/30 (76.7%) men of the control group, the absolute values of serum zinc fitted into the middle–upper tertile of the normal range of the average population reference values (738–1130 mcg/L). Despite such heterogeneity of the control group in absolute serum zinc levels, the average serum zinc level in men of the control group was 844±35 mcg/L, which did not significantly differ from the same value of the average population norm ($p < 0.1$). Thus, the absolute deficiency of serum zinc in healthy men of the control group, according to our data, was 10.0%. In the main group, the absolute level of serum zinc dropped much lower than the lower limiof the general population reference and the absolute values of the control group (<543 mcg/L), reaching a minimum value of 376 mcg/L, which occurred in 26/90 (28.9%) patients. In 36/90 (40.0%) patients of the main group, the absolute values of serum zinc levels were within the lower–middle tercile range of the reference values of the average population norm (543–738 mcg/L), in 21/90 (23.3%) patients, the absolute values of serum zinc levels were within the middle tercile range of the reference values of the average population norm (738–935 mcg/L) and only 7/90 (7.8%) patients with CBP had serum zinc levels, corresponding to the middle–upper terciles of the range of reference values of the average population norm (935–1130 mcg/L). The average serum zinc level in patients of the main group was 720±32 mcg/L, which is significantly lower than the same values in the general population and the control group ($p < 0.05$). Consequently, from the point of view of individual variations in the absolute values of serum zinc concentration, patients with CBP represented a more heterogeneous cohort with a pronounced variance of this parameter compared to healthy men in the control group, and the frequency of detection of absolute serum zinc deficiency in patients with CBP was 28.9%, which is 2.89 times higher than in the control group of healthy men (10.0%, respectively; $p < 0.05$).Since zinc is one of the key cellular and tissue trace elements, where its concentration is several hundred-fold higher than in plasma, the greatest practical interest for urologists is the study of its content in the prostatic fluid, because prostatic gland is the most important physiological consumer of zinc. The absolute zinc concentration in prostatic fluid of healthy men of the control group ranged from 340–670 mcg/ml, averaging 520±53 mcg/ml, which did not significantly differ from the reference values of the average population norm (380–800 mcg/ml and 590±80 mcg/ml, respectively; $p < 0.1$). However, three men of the control group (3/30, or 10.0%), who demonstrated absolute deficiency of serum zinc, simultaneously revealed absolute zinc deficiency in the prostatic fluid. Absolute zinc deficiency in the prostatic fluid was also detected in 2 out of 4 (50.0%) men of the control group with absolute concentration of serum zinc within the lower–middle tertile range of the reference values of the average population norm (6.7%). Thus, the overall detection rate of absolute zinc deficiency in the prostatic fluid in healthy men of the control group was 16.7%. In the patients of the main group, a different zinc metabolism in the prostate gland was observed. Absolute deficiency of prostatic zinc was detected in 37/90 (41.1%) patients with CBP. Conspicuous is the fact of a relatively large proportion of patients with zinc concentration in prostatic fluid within the lower tertile range of reference values of the average population norm (28.9%). In another 24.4% of patients with CBP, individual values of

the prostatic zinc reached the middle tercile of reference values of healthy men, and only in 5.6% of patients with CBP, prostatic zinc reached the upper tercile of reference values of healthy men, which reflects the general decreasing tendency in zinc concentration in prostatic fluid in the cohort of patients with chronic bacterial prostatitis compared with both the average population values, and the values of healthy men of the control group without CBP ($p < 0.05$). In general, from the point of view of individual variations in absolute values of prostatic zinc, patients with CBP represented an even more heterogeneous cohort with a more pronounced variance of this parameter compared with variation in their serum zinc levels, as well as with values of prostatic zinc in men of the control group. At the same time, the detection rate of absolute prostatic zinc deficiency in patients with CBP was 41.1%, which is 2.5 times higher than in healthy men of the control group (16.7%, respectively; ($p < 0.05$)).During the study, we attempted to identify the statistically significant correlation between the zinc concentration in plasma (at the systemic level) and prostatic fluid (at the local organ level) to figure out the diagnostic value of each of them during examination of the patients with CBP. The results of the study showed that in healthy men there was a statistically significant weak positive correlation between the zinc levels in serum and in prostatic fluid ($r = 0.156$; $n = 30$; $p = 0.001$). Within subnormal values (< 543 mcg/L) and lower tercile of reference values of serum zinc (543–738 mcg/L), this correlation was more statistically stronger ($r = 0.204$; $n = 7$; $p = 0.001$), which obviously reflected the absolute deficiency of zinc in the prostatic fluid in 5 out of 7 healthy men (71.4%) with borderline–low levels of serum zinc. The results of studies of correlations between serum and prostatic zinc levels in healthy men showed that its determination in blood serum to establish the sufficiency or deficiency of zinc in the prostatic fluid is not an adequate laboratory test, since the normal (within the known reference values) serum zinc level does not exclude its deficiency in the prostatic fluid, which is probably due to the fact that zinc is, as is known, a cellular and tissue trace element, and its concentration in the blood reflects the presence of a "zinc repository" in the body. The increased requirements of zinc-dependent cells and tissues (and the prostate gland is the most zinc-consuming organ) in this trace element may be accompanied by accelerated consumption of serum zinc, which leads to a decrease in its blood level. Likely, it may be affirmed that the higher the serum zinc level, the greater its repository in the body, the less it is spent on the metabolic needs of cells and tissues; therefore, there is its sufficiency. Confirmation of such conclusions can be the results of correlation studies described above, which showed that the higher diagnostic value is not the absolute level of serum zinc, but the identification, first of all, of the borderline-low level of serum zinc (in the range of subnormal values (<543 mcg/L) and the lower third of the reference values of serum zinc (543–738 mcg/L), in which 71.1% of men in the control group simultaneously revealed a deficiency of prostatic zinc ($p < 0.05$). However, as the results showed, few such men were in the cohort of healthy men in the control group without CBP – 5/30 people, or 16.7% of the total number of the control group. All patients of the main group with absolute deficiency of serum zinc (26 people) and 11 more patients with borderline-low serum zinc levels within the lower third of the reference average population values demonstrated the simultaneous zinc deficiency in the prostatic fluid, and a statistically significant moderate positive correlation was revealed between these indicators ($r = 0.345$; $n = 37$; $p = 0.001$). The study of the relationship between serum and prostatic zinc levels in patients of the main group did not reveal any statistically significant correlation in the middle and upper terciles of the reference values ($p < 0.1$).

Since the intensity of the correlation between the studied parameters in patients of the main group was statistically stronger ($r = 0.345$; $n = 37$; $p = 0.001$) than in men of the control group ($r = 0.204$; $n = 7$; $p = 0.001$) in the borderline-low values of serum zinc concentration, it was concluded that the borderline-low serum zinc level in patients with CBP is the most sensitive and objective marker of prostatic zinc deficiency with a sensitivity close to 100%, unlike the control group, where the sensitivity of this indicator was 71.1% ($p < 0.05$). Thus, it can be assumed that patients with CBP have a physiologically increased requirement for zinc due to its increased consumption by the prostate gland. Therefore, there is not enough time for zinc to accumulate in blood, but it actively enters the prostate gland, and therefore its absolute or relative deficiency in the blood serum persists until the physiological requirements of the prostate gland are met. Obviously, the lower the level of serum zinc is detected in patients with CBP, the more pronounced its deficiency in the prostate tissue. At the same time, a reliable correlation between the concentrations of the serum zinc and zinc in the prostatic fluid was revealed not for all ranges of reference values of serum zinc, but only for its absolutely low (absolute serum deficiency) and borderline-low (in the lower third of normal values) levels in blood serum. Therefore, the most reliable and significant laboratory marker for diagnostics of zinc deficiency in patients with CBP can be considered, first of all, its concentration in the prostatic fluid, rather than in the blood serum. In that regard, later when studying the correlation between the oxidative status of the prostate gland and zinc metabolism disorders in CBP, only the results of assessing the levels of prostatic (in the prostatic fluid) zinc were used for statistical processing as the most objective marker of zinc metabolism in patients with chronic bacterial prostatitis.

The integrative characteristic of clinical and laboratory parameters of CBP depending on the concentration of prostatic zinc is shown in Figs 1–4.

As follows from Figs 1–4, there were statistically significant differences between the control and the main group as a whole, as well as the two comparison groups, after being randomized separately, in the main clinical characteristics of CBP (assessment of the symptoms severity (SS, points), general assessment of symptoms (GAS, points), pain index (PI, points), quality of life index (QLI, points); $p < 0.05$. However, at the same time,

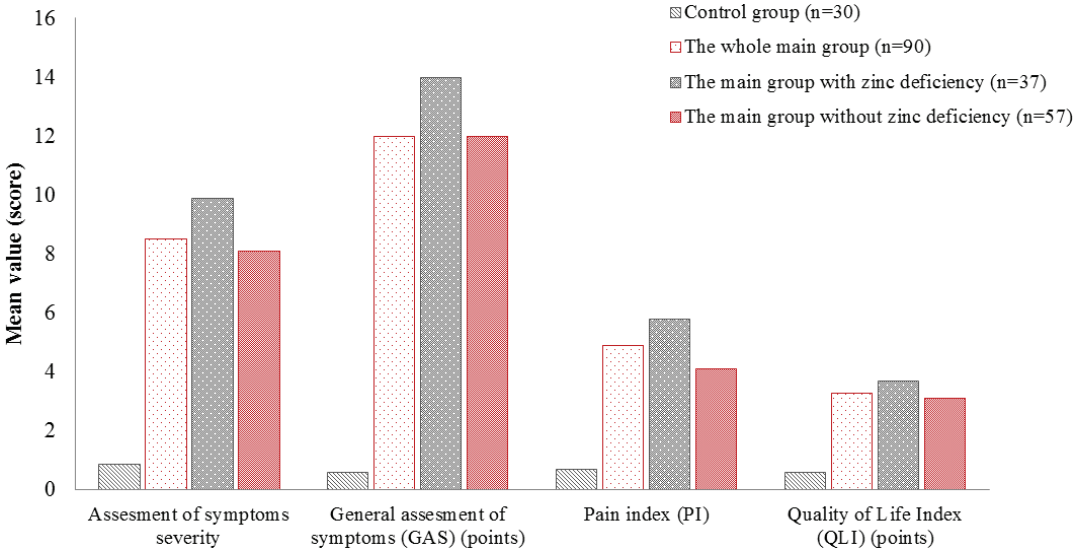

Figure 1. The integrative characteristic of clinical parameters of CBP depending on the concentration of prostatic zinc (n = 120).

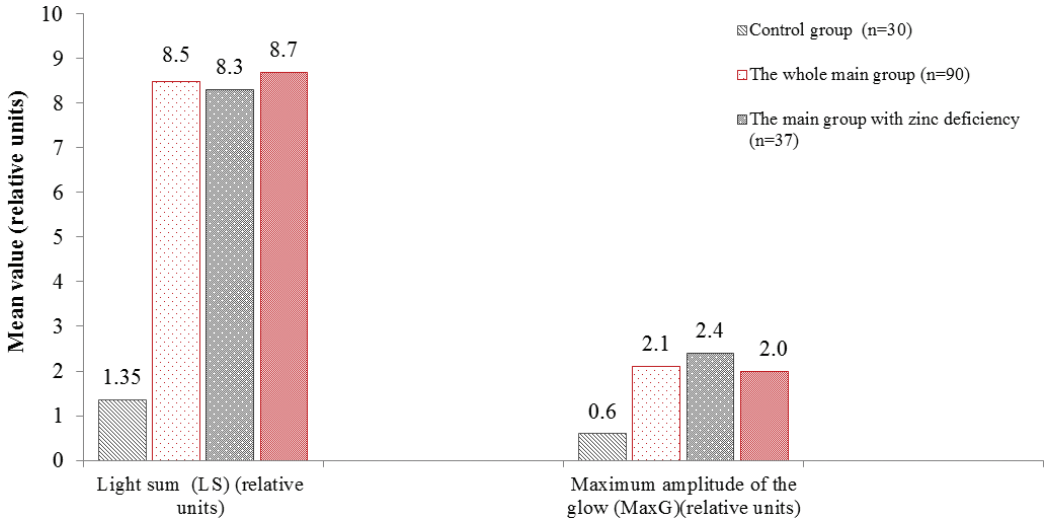

Figure 2. The integrative characteristic of the oxidative status of the prostatic fluid of patients with CBP depending on the concentration of prostatic zinc (n = 120).

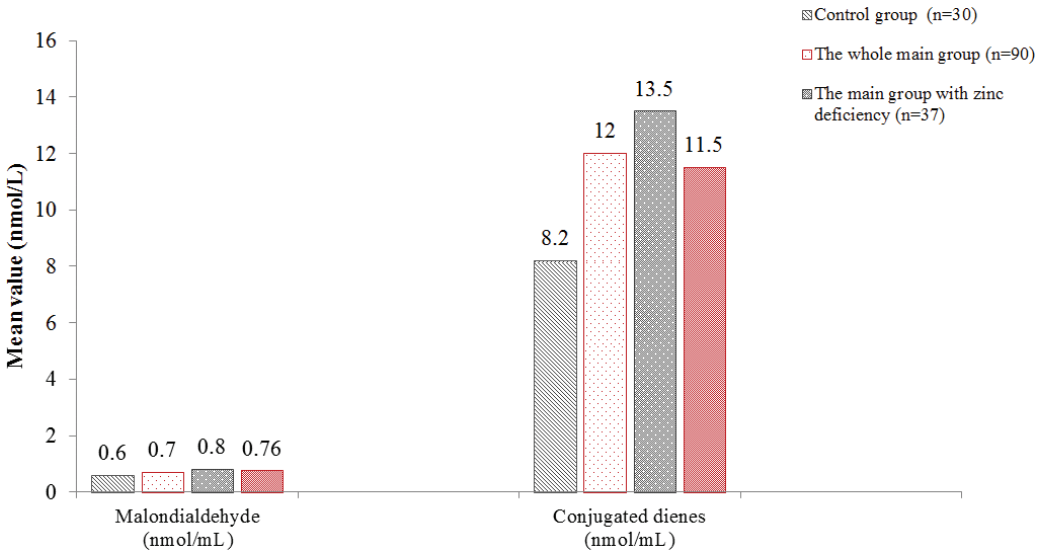

Figure 3. The integrative characteristic of lipid peroxidation in the prostatic fluid of patients with CBP depending on the concentration of prostatic zinc (n = 120).

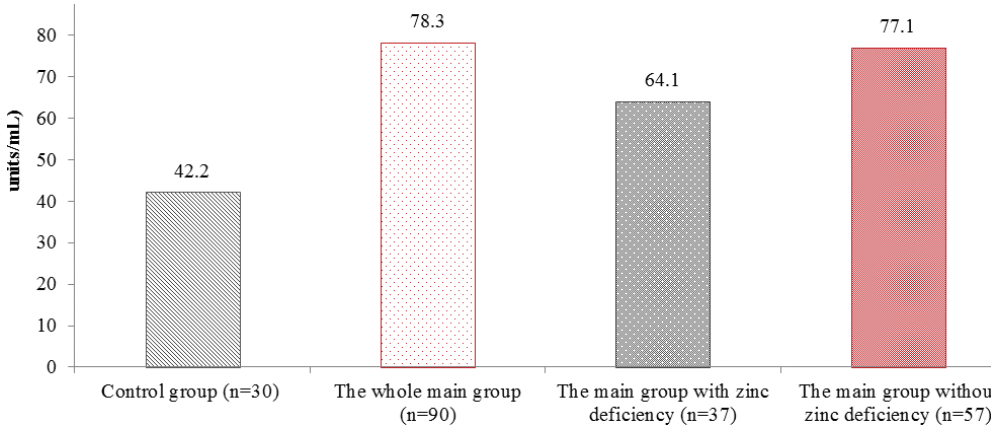

Figure 4. The activity of SOD in the prostatic fluid of patients with CBP depending on the concentration of prostatic zinc (n = 120).

both randomization groups did not significantly differ from each other in their clinical parameters by the presence/absence of prostatic zinc deficiency ($p < 0.1$).

In addition, despite the fact that patients with CBP with prostatic zinc deficiency demonstrated a higher level of leukocytosis in the prostatic fluid, no statistically significant differences were revealed between both randomization groups, most likely due to the pronounced initial variance of the studied parameter in the main group before randomization. Therefore, in this case, obviously, we can talk only about the tendency to increase leukocytosis of prostatic fluid in zinc-deficient patients with CBP compared with the patients without prostatic zinc deficiency ($p < 0.1$).

After randomization of the main group, it was revealed that the secretory function of the prostate gland in patients with CBP and prostatic zinc deficiency was significantly worse than in the whole main group of patients and in patients with CPB without prostatic zinc deficiency ($p < 0.05$). This was evidenced by detecting a low level of lecithin granules in the prostatic fluid, which was diagnosed in 72.9% of patients with prostatic zinc deficiency and only in 61.1% of patients in the main group as a whole and 52.8% of patients without prostatic zinc deficiency, respectively ($p < 0.05$).

The most interesting results were obtained on the oxidative status of the prostate gland in patients with CBP, depending on their prostatic zinc concentration. Thus, the level of free radical aggression in the prostatic fluid in patients with CBP (estimated by the LDCL, reflecting the amount and activity of ROS in the prostatic fluid) remained significantly higher than in the control group of healthy men ($p < 0.05$), but it did not depend on the initial level of zinc in the prostatic fluid.

The study of the lipid peroxidation (LP) in the prostatic fluid established that despite the absence of significant differences in the prostatic concentrations of LP intermediates (conjugated dienes), patients with CBP with prostatic zinc deficiency, unlike zinc-compensated patients with CBP demonstrated a statistically significant increase in the concentration of malondialdehyde in the prostatic fluid, exceeding it by an average of 10.7% for the main group as a whole and by 9.2% for the group of randomization without prostatic zinc deficiency ($p < 0.05$).

The obtained results of the biochemical overreactions of LP, in our opinion, reflected not so much pronounced degree of free radical aggression (since there were no significant differences between the level and activity of ROS in both randomization groups, as mentioned above), but a decrease in the natural resistance of the prostate gland to oxidative stress in concomitant prostatic zinc deficiency.

Confirmation of this assumption was the study results of the activity of superoxide dismutase (SOD) of prostatic fluid, which revealed a statistically significant lower (by 20.2%) activity of this key antioxidant enzyme in patients with CBP with prostatic zinc deficiency compared with the patients with CPB and normal levels of zinc in prostatic fluid ($p < 0.05$). In this context, we considered the decrease in the activity of SOD as a manifestation of the functional insufficiency of the natural antioxidant defense system (ADS) of the prostate gland in conditions of persistent prostatic zinc deficiency, thereby the processes of LP did not carry out all the way through, and the intermediate products of LP (malondialdehyde) overaccumulated in the gland cells. This seemed to be important mechanisms of pathological oxidative stress of the prostate gland mediating the negative effect of the microbial factor on its morpho-functional homeostasis.

In addition to the above, it is worth mentioning that the correlation analysis established a significant moderate positive corellation between the concentration of zinc and the activity of SOD in the prostatic fluid ($r = 0.389$; $n = 90$; $p = 0.001$), which reflected the well-known important physiological role of zinc as one of the most powerful natural prostatic antioxidants.

Conclusion

The study demonstrated a significantly higher frequency of zinc deficiency (both in blood serum and in prostatic fluid) in patients with CBP compared to the population of healthy men. At the same time, the concentration of zinc in the prostatic fluid determines the activity of one of the key specialized enzymes of the antioxidant defense system – superoxide dismutase (SOD), which confirms the critical

physiological role of zinc as a natural prostatic antioxidant and allows us to consider laboratory diagnostics of zinc deficiency and subsequent zinc replacement therapy as effective therapeutic and diagnostic options to improve the results of treatment of CBP. Taking into account the absence of significant correlation between serum and prostatic zinc levels within the entire range of their reference values, as well as in view of the peculiarities of cellular physiology and biochemistry of zinc, the most accurate, optimal and more informative test for routine clinical practice for detecting zinc deficiency is its determination directly in the prostatic fluid in all primary patients with CBP, which at the same time, should be used as a method of the laboratory monitoring of the ongoing compensation of zinc deficiency up to its elimination. Thus, modern pharmacotherapy with zinc supplements in patients with CBP cannot be empirical and chaotic, but should be based on personalized adequate laboratory diagnostics of metabolic disorders of this microelement in each patient, which is important for the prostate gland.

Conflict of interests

The authors declare no conflict of interests.

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