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Review Article

A SYSTEMATIC REVIEW OF THE CHROMIUM CONTENT OF THE NORMAL HUMAN PROSTATE GLAND

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ABSTRACT

The prostate gland is subject to various disorders. The etiology and pathogenesis of these diseases remain not well understood. Moreover, despite technological advancements, the differential diagnosis of prostate disorders has become progressively more complex and controversial. It was suggested that the chromium (Cr) level in prostatic tissue plays an important role in prostatic carcinogenesis and its measurement may be useful as a cancer biomarker. These suggestions promoted more detailed studies of the Cr content in the prostatic tissue of healthy subjects. The present study evaluated by systematic analysis the published data for Cr content analyzed in prostatic tissue of "normal" glands. This evaluation reviewed 1958 studies, all of which were published in the years from 1921 to 2020 and were located by searching the databases PubMed, Scopus, ELSEVIER-EMBASE, Cochrane Library, and the **Web of Science.** The articles were analyzed and "Median of Means" and "Range of Means" were used to examine heterogeneity of the measured Cr content in prostates of apparently healthy men. The objective analysis was performed on data from the 28 studies, which included 1282 subjects. It was found that the range of means of prostatic Cr content reported in the literature for "normal" gland varies widely from 0.009 mg/kg to 0.34 mg/kg with median of means 0.095 mg/kg on a wet mass basis. The level of intra-prostatic metal does not depend on age and androgen status. Finally, because of small sample size and high data heterogeneity, we recommend other primary studies be performed.

Keywords: Chromium, Human prostate, Normal prostatic tissue, Biomarkers.

INTRODUCTION

The prostate gland is subject to various disorders and of them chronic prostatitis, benign prostatic hyperplasia (BPH), and prostate cancer (PCa) are extremely common diseases of aging men [1-3]. The etiology and pathogenesis of these diseases remain not well understood. A better understanding of the etiology and causative risk factors are essential for the primary prevention of these diseases.

In our previous studies, the significant involvement of trace elements (TEs) in the function of the prostate was found. [4-15]. It was also shown that levels of TEs in prostatic tissue, including chromium (Cr), can play a significant role in etiology of PCa [16-20]. Moreover, it was demonstrated that the changes of some TE levels and Zn/TE ratios, including Zn/Cr ratio, in prostate tissue can be used as biomarkers [21-27].

Cr has been studied in medicine since the end of the 19th century, when carcinogenic effects of hexavalent Cr(VI) were discovered. It was indicated very low levels of Cr in human prostatic tissue (0.05 mg/kg of wet tissue) in study published about 60 years ago [28]. However, recently Banaś *et al*. [29] found that the Cr mass fraction in human prostate is two orders of magnitude higher than previously published results (5.0 mg/kg of wet tissue). This finding allowed made the inference that the prostate gland accumulates Cr, because the level of metal in prostate was 50 times higher than the blood serum reference level (0.1 mg/L) [30]. In addition, experimental and epidemiological data identified that Cr, and particularly Cr(VI), should be considered as genotoxic carcinogens [31-36]. According to the International Agency for Research on Cancer and U.S. Environmental Protection Agency, Cr(VI) compounds are classified as Group 1 and Group A human carcinogens, respectively [34]. These findings promoted more detailed studies of the Cr content of prostatic tissue of healthy subjects, as well as of patients with different prostatic diseases, including BPH and PCa.

The effects of TEs, including Cr, are related to their concentration. Recorded observations range from a deficiency state, through normal function as biologically essential components, to an imbalance, when excess of one element interferes with the function of another, to pharmacologically active concentrations, and finally to toxic and even life-threatening concentrations [37]. In this context, low dose of Cr is an essential nutrient for the human body because it is required for normal carbohydrate, lipid, and protein metabolism [38,39]. However, significant Cr exposure may result in adverse health effects in different organs or tissues, including malignancy such as cancers of the lung, nasal and sinus cavities, larynx, stomach, bladder, kidney, testicular, bone, thyroid, as well as PCa [20,31-36]. However, precise molecular mechanisms by which this metal causes healthy cells to transform to malignant states have yet to be fully defined. Multiple mechanisms of carcinogenesis have been proposed involving oxidative stress, DNA damage and genomic instability, and epigenetic modulation [34].

By now, a few studies have reported the Cr content in tissue of "normal" and affected glands. However, further investigation has been considered necessary to provide a practical reference data of Cr levels in prostate norm and disorders, because the findings of various studies indicate some discrepancies.

The present study addresses the significance of Cr levels in prostatic tissue as a biomarker of the gland's condition. Therefore, we systematically reviewed all the available relevant literature and performed a statistical analysis of Cr content in tissue of "normal" glands, which may provide valuable insight into the etiology and diagnosis of prostate disorders.

METHODS

Data sources and search strategy

Aiming at finding the most relevant articles for this review, a thorough comprehensive web search was conducted by consulting the PubMed, Scopus, ELSEVIER-EMBASE, Cochrane Library, and the Web of Science databases, as well as from the personal archive of the author collected between 1966 and 2020, using the key words: Prostatic TEs, prostatic Cr content, prostatic tissue, and their combinations. For example, the search terms for Cr content were: "Cr mass fraction", "Cr content", "Cr level," "prostatic tissue Cr," and "Cr of prostatic tissue." The language of the article was not restricted. The titles from the search results

were evaluated closely and determined to be acceptable for potential inclusion criteria. Furthermore, references from the selected articles were examined as further search tools. Relevant studies noted for the each selected article were also evaluated for inclusion.

Eligibility criteria

Inclusion criteria

Only papers with quantitative data of Cr prostatic content were accepted for further evaluation. Studies were included if the control groups were healthy human males with no history or evidence of urological or other andrological disease and Cr levels were measured in samples of prostatic tissue.

Exclusion criteria

Studies were excluded if they were case reports. Studies involving subjects that were using Cr supplementation or Cr occupational exposed, as well as persons from Cr contaminated area were also excluded.

Data extraction

A standard extraction of data was applied, and the following available variables were extracted from each paper: Method of Cr determination, number and ages of healthy persons, sample preparation, mean and median of Cr levels, standard deviations of mean, and range of Cr levels. Abstracts and complete articles were reviewed independently, and if the results were different, the texts were checked once again until the differences were resolved.

Statistical analysis

Studies were combined based on means of Cr levels in prostatic tissue. The articles were analyzed and "Median of Means" and "Range of Means" were used to examine heterogeneity of Cr contents. The objective analysis was performed on data from the 28 studies, with 1282 subjects.

RESULTS

Information about Cr levels in prostatic tissue in different prostatic diseases is of obvious interest, not only to understand the etiology and pathogenesis of prostatic diseases more profoundly but also for their diagnosis, particularly for PCa diagnosis and PCa risk prognosis [27,37]. Thus, it dictates a need for reliable values of the Cr levels in the prostatic tissue of apparently healthy subjects, ranging from young adult males to elderly persons.

Possible publications relevant to the keywords were retrieved and screened. A total of 1958 publications were primarily obtained, of which 1930 irrelevant papers were excluded. Thus, 28 studies were ultimately selected according to eligibility criteria that investigated Cr levels in tissue of normal prostates (Table 1) and these 28 papers [7,9,11,13,14,24,26,28,29,40-58] comprised the material on which the review was based. A number of values for Cr mass fractions were not expressed on a wet mass basis by the authors of the cited references. However, we calculated these values using the medians of published data for water – 83% [59-62] and ash – 1% (on a wet mass basis) contents in normal prostates of adult men [42,60,63,64].

Table 1 summarizes general data from the 28 studies. The retrieved studies involved 1282 subjects. The ages of subjects were available for 22 studies and ranged from 0 to 87 years. Information about the analytical method and sample preparation used was available for 27 studies. Eight studies determined Cr levels by destructive (require high temperature drying, ashing, acid digestion, or cut section on a cryomicrotome) analytical methods (Table 1): One – proton induced X-ray fluorescence (PIXE), one – inductively coupled plasma mass spectrometry (ICPMS), three – atomic emission spectrometry (AES), and three – synchrotron radiation-induced X-ray emission (SPIXE). Seven studies detected Cr level in intact prostatic tissue samples by nondestructive analytical method, such as neutron activation analysis (NAA). In 12 studies a combination of destructive and nondestructive methods (ICPMS and NAA) was used and results were summarized.

Fig. 1 illustrates the data set of Cr measurements in 28 studies during the period from 1956 to 2020.

DISCUSSION

The range of means of Cr mass fractions reported in the literature for "normal" prostatic tissue varies widely from 0.009 mg/kg [42] to 5.0 mg/kg [29] with median of means 0.0955 mg/kg of wet tissue (Table 1). Some maximal values of mean Cr mass fraction reported 5.0 mg/kg [29], 1.3 [44], and 2.6 [45] were at least one order of magnitude higher than the median (0.0955 mg/kg of wet tissue). The mean ± standard deviation (M±SD) of all other published means was 0.102±0.056 mg/kg of wet tissue. Because values 5.0 mg/kg [29], 1.3 [44], and 2.6 [45] were higher the level "M +20SD," they can be excluded. However, without these extremal results range of means of Cr mass fractions for "normal" prostatic tissue remains very wide from 0.009 mg/kg [42] to 0.34 mg/kg [43] with median of means 0.095 mg/kg of wet tissue and M_{max}/M_{min} ratio approximately 38 (Table 1).

This variability of reported mean values can be explained a priori by a dependence of Cr content on many factors, including analytical method imperfections, differences in "normal" prostate definitions, possible non-homogeneous distribution of Cr levels throughout the prostate gland volume, age, ethnicity, diet, smoking, alcohol intake, consuming supplemental TEs, and others. Not all these factors were strictly controlled in the cited studies. For example, in some studies the "normal" prostate means a gland of an apparently healthy man who had died suddenly, but without any morphological confirmation of "normality" of his prostatic tissue. In other studies, the "normal" prostate means a non-cancerous prostate (but hyperplastic and inflamed glands were included) and even a visually normal prostatic tissue adjacent to a prostatic malignant tumor. Some researchers used as the "normal" prostate the glands of patients who died from acute and chronic non-prostatic diseases including subjects who had suffered from prolonged wasting illnesses. In some studies, whole glands were used for the investigation while in others the Cr content was measured in pieces of the prostate. Therefore, published data allowed us to estimate the effect of only some different factors on Cr content in "normal" prostate tissue.

Analytical method

The trend line of Cr content data in "normal" prostate (Fig. 1) showed that an improvement of analytical technologies during last almost 60 years did not impact significantly on the means and variability of reported values. Thus, in our opinion, the leading cause of inter-observer variability was insufficient quality control of results in published studies. In some reported papers such destructive

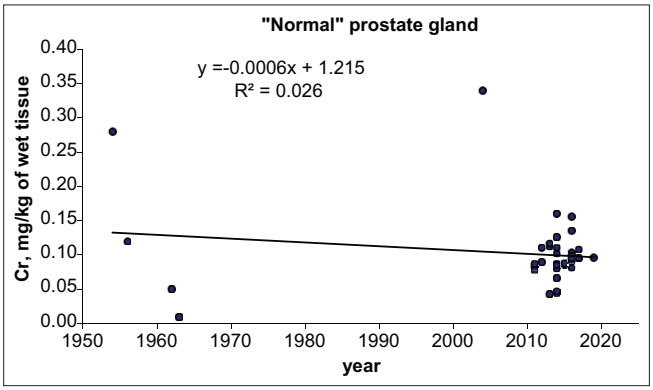

Fig. 1: Data on Cr content in normal prostate tissue reported from 1954 to 2020 without values 5.06 mg/kg [29], 1.36 mg/kg [44], and 2.6 mg/kg of wet tissue [45]

Table 1: Reference data of Cr mass fractions (mg/kg wet tissue) in "normal" human prostate

Reference	Method	n	Age range years	Sample preparation	Cr	
					M±SD	Range
Tipton *et al*., 1954 [40]	AES	8	Adult	D, A	0.28	-
Koch *et al*., 1956 [41]	AES	4	Adult	AD	0.12	-
Zakutinsky *et al*., 1962 [28]	-	-	-	-	0.05	-
Tipton *et al*., 1963 [42]	AES	50	Adult	D, A	0.009 Median	Max=0.023
Banaś *et al*., 2001 [29]	SRIXE	5	Adult	CS (NB)	5.0±1.0	-
Kwiatek *et al*., 2004 [43]	SRIXE	3	61	CS (NB)	0.34±0.09	-
Kwiatek *et al*., 2005 [44]	SRIXE	1	Adult	CS (NB)	1.3	
Guntupalli *et al*., 2007 [45]	PIXE	27	38–68	H, Pressing	2.6±1.6	-
Zaichick and Zaichick, 2011 [46]	NAA	64	13–60	Intact	0.082±0.079	0.005-0.32
		9	13–20	Intact	0.082±0.077	-
		28	21–40	Intact	0.078±0.068	-
		27	41–60	Intact	0.087±0.077	-
Zaichick and Zaichick, 2012 [24]	NAA	37	66±8	Intact	0.090±0.071	0.005–0.31
Zaichick *et al*., 2012 [47]	ICPMS	64	13–60	AD	≤DPMS	<0.085–0.32
Zaichick and Zaichick, 2013 [7]	NAA	29	0–13	Intact	0.112±0.085	-
		21	14–30	Intact	0.043±0.036	-
Zaichick and Zaichick, 2013 [9]	2 Methods	29	0–13	Intact	0.117±0.087	-
		21	14–30	Intact	0.043±0.031	-
Zaichick and Zaichick, 2014 [48]	NAA	28	21–40	Intact	0.066±0.049	0.008–0.167
		27	41–60	Intact	0.087±0.075	0.005–0.31
		10	61–87	Intact	0.102±0.068	0.048–0.24
Zaichick and Zaichick, 2014 [49]	2 Methods	28	21–40	Intact, AD	0.080±0.079	0.008–0.32
		27	41–60	Intact, AD	0.085±0.066	0.005–0.31
		10	61–87	Intact, AD	0.126±0.090	0.049–0.27
Zaichick and Zaichick, 2014 [11]	NAA	29	0–13	Intact	0.16±0.13	
		21	14–30	Intact	0.047±0.040	
		50	0–30	Intact	0.11±0.11	
Zaichick and Zaichick, 2014 [13]	2 Methods	16	20–30	Intact, AD	0.044±0.029	-
Zaichick and Zaichick, 2014 [14]	2 Methods	50	0–30	Intact, AD	0.11±0.12	
		29	0–13	Intact, AD	0.16±0.13	
		21	14–30	Intact, AD	0.047±0.035	
Zaichick and Zaichick, 2015 [50]	NAA	32	44–87	Intact	0.085±0.058	0.005–0.24
Zaichick, 2015 [51]	2 Methods	65	21–87	Intact, AD	0.088±0.071	-
Zaichick and Zaichick, 2016 [52]	NAA	28	21–40	Intact	0.081±0.058	0.012–0.190
		27	41–60	Intact	0.100±0.098	0.007–0.370
		10	61=87	Intact	0.135±0.104	0.073–0.347
Zaichick and Zaichick, 2016 [53]	2 Methods	65	21–87	Intact, AD	0.104±0.083	0.007–0.370
		28	21–40	Intact, AD	0.093±0.015	-
		27	41–60	Intact, AD	0.099±0.016	-
		10	61=87	Intact, AD	0.156±0.041	-
Zaichick and Zaichick, 2016 [54]	2 Methods	32	44–87	Intact, AD	0.090±0.068	-
Zaichick and Zaichick, 2016 [55]	2 Methods	37	41–87	Intact, AD	0.095±0.082	-
Zaichick and Zaichick, 2017 [26]	2 Methods	37	41–87	Intact, AD	0.095±0.082	-
Zaichick and Zaichick, 2017 [56]	2 Methods	37	41–87	Intact, AD	0.108±0.082	0.0068–0.352
Zaichick, 2017 [57]	2 Methods	37	41–87	Intact, AD	0.096±0.074	0.005–0.31
Zaichick and Zaichick, 2019 [58]	2 Methods	37	41–87	Intact, AD	0.096±0.074	0.005–0.31
Median of means		0.0955 or 0.095 (without 5.0, 1.3, 2.6)				
Range of means (M_{min}–M_{max})		0.0090–5.0 or 0.0090–0.34 (without 5.0, 1.3, 2.6)				
Ratio M_{max}/M_{min}		556 or 37.8 (without 5.0, 1.3, 2.6)				
All references		28				

M: Arithmetic mean, SD: Standard deviation of mean, AES: Atomic emission spectrometry, SRIXE: Synchrotron radiation-induced X-ray emission, PIXE: Proton induced X-ray fluorescence, NAA: Neutron activation analysis, ICPMS: Inductively coupled plasma mass spectrometry; 2 Methods: NAA and ICPMS, D: Drying at high temperature, A: Ashing, AD: Acid digestion, CS: Cut section on a cryomicrotome, NB: Needle biopsy, H: Homogenization

analytical methods as AES [40-42] and ICP-MS [47] were used. These methods require ashing and acid digestion of the samples at a high temperature. There is evidence that use of this treatment causes some quantities of TEs to be lost [37,65,66]. On the other hand, the Cr content of chemicals used for acid digestion can contaminate the prostate samples. Thus, when using destructive analytical methods it is necessary to allow for the losses of TEs, for example, when there is complete acid digestion of the sample. Then, there are contaminations by TEs during sample decomposition, which require addition of some chemicals.

Such destructive analytical method as SRIXE [29,43,44] needs in cutting section on a cryomicrotome, and PIXE [45] – in a tissue sample homogenization and slice pressing. In these cases samples may be contaminated during sample preparation, because a blade of microtome and a press made of Cr-contained stainless steel needs to use [67].

It is possible to avoid these problems using non-destructive methods, such as NAA [7,11,24,46,48,50,52] which allow quantify Cr content in "normal" prostate without any sample preparation. Moreover, a good agreement between results obtained by both NAA and ICPMS methods under a strong quality control [9,13,14,26,49,51,53-58] shoved that in case of Cr it is possible to avoid uncertainties connected with acid digestion. It is, therefore, reasonable to conclude that the quality control of results is very important factor for using the Cr content in prostatic tissue as biomarkers.

Age

In a few studies, it was found that the prostatic Cr content does not depend on age during lifespan. It was shown by the comparison of different age groups or the Pearson's coefficient of correlation between age and Cr content in prostate tissue [7,9,11,14,46,48,49,52,53].

Androgen-independence of prostatic Cr level

There was not found any statistical significant difference between Cr levels in prostates of teenagers before puberty and of post-pubertal teenagers and young adults [7,9,11,14]. These findings allowed us to conclude that the Cr content in "normal" prostates does not depend on the level of androgens, and vice versa. However, studies on the association between the Cr content in "normal" prostates and the level of androgens in blood were not found.

Cr intake

The general population can be exposed to low levels of Cr primarily through consumption of food and to a lesser degree through inhalation of ambient air and ingestion of drinking water [33]. Vegetables (broccoli, green beans, and potatoes), fruits (apples, bananas, peas, ad grapes), kidney, liver, meats, poultry, seafood, and cheese generally contain the most Cr [68]. For most of the general population, dietary intake (50–200 μg Cr/d) represents the primary source of Cr exposure [38]. Elevated Cr intake may result from prescription Cr supplements. Other potential sources of Cr exposure include consumer products, automobile exhaust, and smoking, including traditional and electronic cigarettes and hookahs [34]. However, over the last decade**s**, the use of Co-Cr hard-metal alloys in orthopedic arthroplasties has created an entirely new source of internal Cr exposure. Orthopedic arthroplasties are artificial devices made of Co-Cr alloys which are used to replace damaged joints in the body, for example, hip, knee, finger, and shoulder. If these orthopedic devices were initially mainly used by the elderly, but now they are used in increasing numbers across the populace. About 0.16–0.2% of population per year in industrial countries undergo only total hip joint arthroplasty and the recipients are from all age groups ranging from 20 to 80 years of age [69]. Corrosion and wear produce soluble metal ions and metal debris in the form of huge numbers of wear particles in nanometric size, with systemic dissemination through lymph, and systemic vascular system [70].

Cr content in body fluids, tissues, and organs

It is known that Cr is accumulated primarily in liver, kidney, and muscle [70]. Mass fraction of this metal in the liver of Reference Man ranged from 0.005 to 0.050 (mean 0.01) mg/kg of wet tissue [30]. The median of prostatic Cr content means obtained in the present review (0.095 mg/kg of wet tissue) is almost one order of magnitude higher the metal level in liver. Thus, we can conclude that the prostate is a target organ for Cr and a small increase of Cr concentration in blood for a long period may associate with a great increase of this metal in different target organs, including the prostate.

All natural chemical elements of the Periodic System, including Cr, present in all subjects of biosphere [37,71,72]. During the long evolutional period intakes of Cr were more or less stable and organisms were adopted for such environmental conditions. Moreover, organisms, including human body, involved low doses of this metal in their functions. For example, Cr is biologically active as part of an oligopeptide – chromodulin – potentiating the effect of insulin by facilitating insulin binding to receptors at the cell surface [39]. The situation began to change after the industrial revolution, particularly, over the past 100 years. Discovered in the 1797 year, the use of Cr and various Cr compounds and alloys started to become industrially important near the close of the 19th century. Cr is the 21st most common element found in the earth's crust, but it is not found in its free metal form. Instead, it is principally found in chromite ore. Cr metal is obtained by heating the chromite ore in the presence of aluminum or silicon.

Cr and Cr compounds are consumed by the chemical, metallurgical, and refractory industries. Major uses for metallic Cr include chrome electroplating and production of stainless steel. Stainless steel is an alloy of iron and at least 10.5% Cr. Cr compounds are used as pigments for glass, ceramics, and enamels, as driers for paints, varnishes, or lacquers. About 90% of leather is Cr sulfate tanned. The textile industry uses Cr ions to adhere dyes to fabric. Kilns and furnaces use bricks made of chromite ore, which retains strength at high temperatures [73].

The extensive use of Cr in various industrial processes increases the levels of pollution in the environment. Environmental Cr pollution occurs mainly through a combination of air, water, and land contamination and is subsequently introduced into the food chain. Cr and its compounds are released into the air as by-products of fossil fuel combustion, waste incineration, and various industrial processes (e.g., aerospace products and parts manufacturing, pulp and paper mills, ferro Cr or Cr metal production) as diffused pollution [74]. Cr is discharged into the water in the form of wastewater from industries such as leather tanning, metal fabrication, and Cr plating, as well as from production of wood preservatives, chrome pigments (e.g., lead chromate) which are used in paints, printing inks, and anti-corrosive materials [74]. Cr in the soil may come from atmospheric deposition, sediment accumulation, and the potential leach ability of this metal [74].

Of the estimated 2700–2900 metric tons of Cr emitted to the atmosphere annually from anthropogenic sources in the United States, approximately one-third is in the hexavalent form [75]. The global demand for Cr increases constantly and, as the consequence of it, concentrations of this metal in the environmental media also increase. Thus, it is likely that Cr content in the "normal" prostate tissue will increase as the result of a global accumulation of Cr in the environment.

Thus, according our study for not polluted areas no one influencing factor could explain the variability of published means for prostatic Cr levels from 0.0090 mg/kg to 0.34 mg/kg in wet tissue. Moreover, prostate tissue Cr contents showed large variations among individuals, but sources of the variation remain unknown. It is reasonable to assume from data of our study that inaccuracy of analytical technologies employed caused so great variability of published means for prostatic Cr levels. This conclusion was supported the fact that the Certified Reference Materials for quality control of results were not used in studies reported in 1960s [40-42] and in 2000s [29,43-45].

There are some limitations in our study, which need to be taken into consideration when interpreting the results of this review. The sample size of each study was sometimes relatively small (from 1 to 65), and a total of 1282 "normal" controls were investigated from all 28 studies. As such, it is hard to draw definite conclusions about the reference value of the Cr content in "normal" prostate as well as about the clinical value of the Cr levels in "normal" prostates as a biomarker.

CONCLUSION

The present study is a comprehensive study regarding the determination of Cr content in "normal" human prostates. With this knowledge Cr levels may then be considered as a biomarker for the recognition of prostate disorders. The study has demonstrated that level of Cr in "normal" prostates depends on analytical method. Because of the uncertainties we have outlined, we recommend other primary studies be performed.

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