REVIEW ARTICLE

A Systematic Review of the Cobalt Content of the Normal Human Prostate Gland

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ABSTRACT

Background: 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 cobalt (Co) 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 Co content in the prostatic tissue of healthy subjects. **Materials and Methods:** The present study evaluated by systematic analysis the published data for Co content analyzed in prostatic tissue of "normal" glands. This evaluation reviewed 1949 studies, all of which were published in the years from 1921 to 2020 and were located by searching the databases Scopus, PubMed, MEDLINE, 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 Co content in prostates of apparently healthy men. The objective analysis was performed on data from the 23 studies, which included 1207 subjects. **Results:** It was found that the range of means of prostatic Co content reported in the literature for "normal" gland varies widely from 0.0035 mg/kg to 0.11 mg/kg with median of means 0.0077 mg/kg on a wet mass basis and the level of intraprostatic metal increases with age in adults. **Conclusions:** Because of small sample size and high data heterogeneity, we recommend other primary studies be performed.

Key words: Biomarkers, cobalt, human prostate, normal prostatic tissue

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 ageing men.[1-3] The etiology and pathogenesis of these diseases remain not well understood. A better understanding of the etiology and causative risk factors is 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 cobalt (Co), can play a significant role in etiology of PCa.[16-20] Moreover, it was demonstrated that the changes of some TE levels and Co/TE ratios in prostate tissue can be used as biomarkers.[21-28]

It was indicated very low levels of Co in human prostatic tissue (<0.02 mg/kg wet tissue) in studies published more than 55 years ago.[29,30] However, recently, Kwiatek *et al*.[31] found that the Co mass fraction in human prostate is two orders of magnitude higher than previously published results (3.8 mg/kg wet tissue). This finding allowed conclude that the prostate gland accumulates Co, because the levels of metal in prostates were about four orders of magnitude higher than the blood serum reference level (<0.0003 mg/L).[32] Furthermore, experimental and epidemiological data identified that Co

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compounds should be considered as genotoxic carcinogens with a practical threshold.[33] Consequently, the International Agency for Research on Cancer has evaluated Co as carcinogenic to humans.[34] Humans are exposed to Co from industry and surgical devices, most notably orthopedic joint replacements made of Co-Cr hard metal alloys. Many epidemiologic and laboratory studies found that total joint arthroplasty increases the risk of cancer and particularly Pca.[35-40] These findings promoted more detailed studies of the Co 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 Co, 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.[41] In this context, for example, Vitamin B12 is an essential Co-containing nutrient and the human body needs in it in low dose, but significant Co exposure may result in adverse health effects in different organs or tissues, including malignancy such as multiple myeloma, tongue cancer, and Pca.[35-40,42,43] However, precise molecular mechanisms by which this metal causes healthy cells to transform to malignant states have yet to be fully defined. Current models propose the induction of reactive oxygen species (ROS) and oxidative DNA damage by ROS, combined with inhibition of DNA repair.[38]

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

The present study addresses the significance of Co 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 Co content in tissue of "normal" glands, which may provide valuable insight into the etiology and diagnosis of prostate disorders.

MATERIALS AND 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 Scopus, PubMed, MEDLINE, 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 Co content, prostatic tissue, and their combinations. For example, the search terms for Co content were "Co mass fraction," "Co content," "Co level," "prostatic tissue Co," and "Co 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 Co 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 Co levels were measured in samples of prostatic tissue.

Exclusion criteria

Studies were excluded if they were case reports. Studies involving subjects that were using Co supplementation or Co occupational exposed, as well as persons from Co 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 Co determination, number and ages of healthy persons, sample preparation, mean and median of Co levels, standard deviations of mean, and range of Co 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 Co levels in prostatic tissue. The articles were analyzed and "Median of Means" and "Range of Means" were used to examine heterogeneity of Co contents. The objective analysis was performed on data from the 23 studies, with 1207 subjects.

RESULTS

Information about Co 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.[27,28,41] Thus, it dictates a need for reliable values of the Co 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 1949 publications were

primarily obtained, of which 1926 irrelevant papers were excluded. Thus, 23 studies were ultimately selected according to eligibility criteria that investigated Co levels in tissue of normal prostates [Table 1] and these 23 papers[7,9,11,13,14,24,26,29-31,44-56] comprised the material on which the review was based. A number of values for Co 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%[57-60] and ash – 1% (on a wet mass basis) contents in normal prostates of adult men.[30,44,59,61] Table 1 summarizes general data from the 23 studies. The retrieved studies involved 1207 subjects. The ages of subjects were available for 19 studies and ranged from 0 to 87 years. Information about the analytical method and sample preparation used was available for 22 studies. Four studies determined Co levels by destructive (require high temperature drying, ashing, acid digestion, or cut section on a cryomicrotome) analytical methods [Table 1]: One – atomic emission spectrometry (AES), one – atomic absorption spectrophotometry (AAS), one – synchrotron radiation-induced X-ray emission, and one – inductively coupled plasma mass spectrometry (ICPMS). Six studies detected Co level in intact prostatic tissue samples by non-destructive analytical method, such as neutron activation analysis (NAA). In 12 studies, a combination of destructive and non-destructive methods (ICPMS and NAA) was used and results were summarized.

DISCUSSION

The range of means of Co mass fractions reported in the literature for "normal" prostatic tissue varies widely from 0.0035 mg/kg[49] to 3.8 mg/kg[31] with median of means 0.0078 mg/kg wet tissue [Table 1]. The maximal value of mean Co mass fraction reported[31] was 487 times higher the median of Co mass fraction means and at least one order of magnitude higher than all other published means. Thus, value 3.8 mg/kg[31] can be excluded. However, without this result, range of means of Co mass fractions for "normal" prostatic tissue remains very wide from 0.0035 mg/kg[49] to 0.11 mg/kg[44] with median of means 0.0077 mg/kg wet tissue and M_{max}/M_{min} ratio approximately 31 [Table 1].

This variability of reported mean values can be explained a priori by a dependence of Co content on many factors, including analytical method imperfections, differences in "normal" prostate definitions, possible non-homogeneous distribution of Co 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 Co content was measured in pieces of the prostate. Therefore, published data allowed us to estimate the effect of only some different factors on Co content in "normal" prostate tissue.

Analytical method

The trend line of Co content data in "normal" prostate [Figure 1] showed that an improvement of analytical technologies during the last 58 years impacted significantly on the mean and variability of reported values. In our opinion, the leading cause of interobserver variability was an insufficient sensitivity of analytical techniques and a lack of quality control of results in old studies published in 60s.

In some reported papers, such destructive analytical methods as AES, AAS, and ICP-MS were used. These methods require acid digestion of the samples at a high temperature. There is evidence that the use of this treatment causes some quantities of TEs to be lost.[41,62,63] On the other hand, the Co 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. In the case of a paraffin/epoxy-embedded tissue samples, Co, particularly from prostatic fluid, may be lost during sample fixation in ethanol/chloroform/formaldehyde.

It is possible to avoid these problems using non-destructive methods, such as NAA, which allow to quantify Co content in "normal" prostate without acid digestion. Moreover, a good agreement between results obtained by both NAA and ICPMS methods under a strong quality control[9,13,14,26,48,49,51-56] shoved that in case of Co, 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 Co content in prostatic tissue as biomarkers.

Age

In a few studies, a significant increase in Co content with increasing of age of adults was shown by the comparison of different age groups or the Pearson's coefficient of correlation between age and Co content in prostate tissue.[47-51] For example, a strongly pronounced tendency for an age-related exponential increase of Co mass fraction was observed in the prostate for the third to eighth decades.[48] In prostates

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

Reference	Method	*n*	Age range years	Sample preparation	Co	
					Mean±SD	Range
Zakutinsky *et al.*, 1962[29]	-	-	-	-	<0.07	-
Tipton *et al.*, 1963[30]	AES	50	Adult	D, A	<0.02	Max=0.03
Schroeder *et al.*, 1967[44]	AAS	1	Adult	A, AD	0.11	-
Kwiatek *et al.*, 2005[31]	SRIXE	1	Adult	CS (NB)	3.8	-
Zaichick *et al.*, 2011[45]	NAA	64	13–60	Intact	0.0061±0.0037	0.0014–0.0180
		9	13–20	Intact	0.0051±0.0031	-
		28	21–40	Intact	0.0051±0.0026	-
		27	41–60	Intact	0.0080±0.0043	-
Zaichick *et al.*, 2012[24]	NAA	37	66±8	Intact	0.0077±0.0041	0.0028–0.0180
Zaichick *et al.*, 2012[46]	ICPMS	64	13–60	AD	0.0077±0.0041	0.0024–0.0180
Zaichick *et al.*, 2013[7]	NAA	29	0–13	Intact	0.0077±0.0054	-
		21	14–30	Intact	0.0039±0.0017	-
Zaichick *et al.*, 2013[9]	2 methods	16	0–13	Intact, AD	0.0075±0.0054	-
			14–30	Intact, AD	0.0077±0.0041	-
Zaichick *et al.*, 2014[47]	NAA	28	21–40	Intact	0.0049±0.0026	0.0013–0.0125
		27	41–60	Intact	0.0080±0.0044	0.0028–0.0180
		10	61–87	Intact	0.0070±0.0026	0.0039–0.0100
Zaichick *et al.*, 2014[48]	2 methods	28	21–40	Intact, AD	0.0053±0.0024	0.0023–0.0129
		27	41–60	Intact, AD	0.0073±0.0039	0.0028–0.0180
		10	61–87	Intact, AD	0.0095±0.0095	0.0034–0.0340
Zaichick *et al.*, 2014[11]	NAA	29	0–13	Intact	0.0100±0.0074	-
		21	14–30	Intact	0.0046±0.0023	-
		50	0–30	Intact	0.0076±0.0063	-
Zaichick *et al.*, 2014[13]	2 methods	16	20–30	Intact, AD	0.0041±0.0016	-
Zaichick *et al.*, 2014[14]	2 methods	50	0–30	Intact, AD	0.0077±0.0060	-
		29	0–13	Intact, AD	0.0099±0.0072	-
		21	14–30	Intact, AD	0.0050±0.0023	-
Zaichick, 2015[49]	2 methods	28	21–40	Intact, AD	0.0035±0.0031	0.0023–0.0129
		27	41–60	Intact, AD	0.0073±0.0039	0.0028–0.0180
		10	61–87	Intact, AD	0.0095–0.0095	0.0034–0.0340
		37	41–87	Intact, AD	0.0080±0.0060	0.0028–0.0340
Zaichick *et al.*, 2016[50]	NAA	28	21–40	Intact	0.0060±0.0032	0.0014–0.146
		27	41–60	Intact	0.0097±0.0055	0.0029=0.0227
		10	61=87	Intact	0.0088±0.0055	0.0050–0.0129
Zaichick *et al.*, 2016[51]	2 methods	65	21–87	Intact, AD	0.0081±0.0032	0.0025–o.0418
		28	21–40	Intact, AD	0.0062±0.00813	-
		27	41–60	Intact, AD	0.0089±0.0052	-
		10	61=87	Intact, AD	0.0120±0.0123	-
Zaichick *et al.*, 2016[52]	2 methods	32	44–87	Intact, AD	0.0078±0.0064	-
Zaichick *et al.*, 2016[53]	2 methods	37	41–87	Intact, AD	0.0080±0.0060	-
Zaichick *et al.*, 2017[26]	2 methods	37	41–87	Intact, AD	0.0080±0.0060	-
Zaichick *et al.*, 2017[54]	2 methods	37	41–87	Intact, AD	0.0093±0,0070	0.00272–0.0398

(Contd...)

Table 1: (*Continued*)

Reference	Method	*n*	Age range years	Sample preparation	Co	
					Mean±SD	Range
Zaichick, 2017[55]	2 methods	37	41–87	Intact, AD	0.0080±0.0060	0.0028–0.0340
Zaichick *et al.*, 2019[56]	2 methods	37	41–87	Intact, AD	0.0080±0.0060	0.0028–0.0340
Median of means	0.0078 or 0.0077 (without 3.8)					
Range of means (M_{min}–M_{max})	0.0035–3.8 or 0.0035–0.11 (without 3.8)					
Ratio M_{max}/M_{min}	1086 or 31.4 (without 3.8)					
All references	23					

M: Arithmetic mean, SD: Standard deviation of mean, AES: Atomic emission spectrometry, AAS: Atomic absorption spectrophotometry, SRIXE: Synchrotron radiation-induced X-ray emission, 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

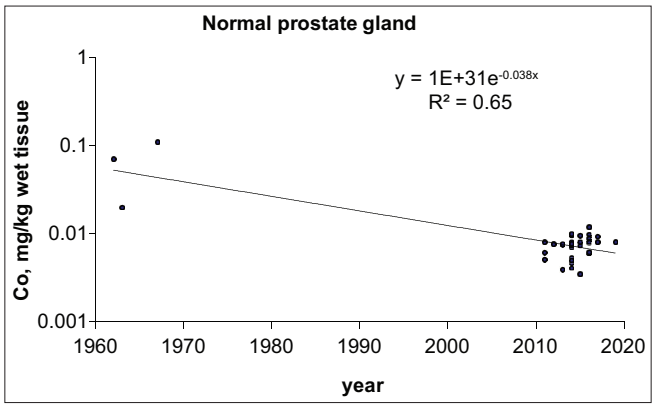

Figure 1: Data on cobalt content in normal prostate tissue reported from 1962 to 2020 without value 3.8 mg/kg wet tissue published in 2005[31]

of 61–87 years old men, the mean Co mass fraction was 2–3 times greater than that in the prostates of 21–40 years old males.[48,49,51] Thus, the accumulated information, studied by us from reported data, allowed a conclusion that there is a significant exponential increase in Co mass fraction in "normal" prostate from age 21 years to the eighth decade.

Androgen independence of prostatic Co levels

There was not found any difference between Co 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 Co content in "normal" prostates does not depend on the level of androgens and vice versa. However, studies on the association between the Co content in "normal" prostates and the level of androgens in blood were not found.

Co intake

The general population can be exposed to low levels of Co primarily through consumption of food and to a lesser degree through inhalation of ambient air and ingestion of drinking water.[64] Green, leafy vegetables and fresh cereals generally contain the most Co.[34] For most of the general population, dietary intake (5–40 μg Co/d) represents the primary source of Co exposure. Elevated Co intake may result from prescription Vitamin B12 or other mineral preparations containing Co compounds. Other potential sources of Co exposure include consumer products and tobacco smoking.[64] However, over the past decades, the use of Co hard metal alloys in orthopedic joint replacements, in particular in metal-on-metal bearings in hip joint arthroplasty, has created an entirely new source of internal Co exposure. 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.[64]

Co content in body fluids, tissues, and organs

It is known that Co is accumulated primarily in liver, kidney, pancreas, heart, skeleton, and muscle.[38] Mass fraction of this metal in liver ranged from 0.006 to 0.045 (mean 0.018) mg/kg wet tissue.[65] The median of prostatic Co content means obtained in the present review is very close to the metal level in liver. Thus, we can conclude that the prostate is also a target organ for Co. A small increase of Co intake for a long period associated with a great increase of metal concentration in blood,[66] and, as a consequence in different organs, including the prostate.

All natural chemical elements of the periodic system, including Co, present in all subjects of biosphere.[41,67,68] During the long evolutional period, intakes of Co 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, Co is a part of Vitamin B12.[69] The situation began to change after the industrial revolution, particularly, over the past 100 years. Discovered in the 1735 year, the use of Co and various Co compounds and alloys started to become industrially important near the close of the 19th century. Co metal is produced as a by-product from ores associated with Cu, Ni, Zn, Pb, and Pt group metals and is most often chemically combined in its ores

with S and As. Co and Co compounds are used in numerous commercial, industrial, and military applications. Major uses for metallic Co include production of superalloys, cemented carbides, and bonded diamonds. Co nanoparticles are used in medical applications (e.g., sensors, magnetic resonance imaging contrast enhancement, and drug delivery), and Co nanofibers and nanowires are used in industrial applications. Co compounds are used as pigments for glass, ceramics, and enamels, as driers for paints, varnishes, or lacquers, as catalysts, as adhesives and enamel frits, and as trace mineral additives in animal diets. The fastest-growing use for Co in recent years has been in high-capacity, rechargeable batteries for electric vehicles and portable electronic devices such as smartphones and laptops. Environmental Co pollution occurs mainly through a combination of land (through atmospheric emissions originating from residues from coal, oil, and gas combustion, urban refuse, mine tailings and smelter slag, and also from waste, fertilizers, and sludge application), water (through irrigation and industrial liquid waste), and air (through atmospheric industrial emissions and vehicle exhaust) contamination and is subsequently introduced into the food chain. Worldwide, in the end of 20th century, approximately 75,000 metric tons of Co enters the environment annually, with similar amounts coming from natural sources (40,000 metric tons) and sources related to human activities (35,000 metric tons), and global demand for metal increased constantly. Moreover, it is likely that this tendency will continue. Age-dependent increase of Co mass fractions in the "normal" prostate tissue indirectly confirms this conclusion. As was highlight above, age-dependent increase of Co mass fractions in the "normal" prostate over lifespan of adults is more ideally fitted by an exponential law than by a linear, polynomial, logarithmic, or power law.[45-51] If an exponential increase of Co in prostate of healthy men living in a non-industrial, ecologically safe region will be confirmed, this could be interpreted as the result of a global increase of the concentrations of Co in the environment. Thus, according our study for not polluted areas, no one influencing factor could explain the variability of published means for prostatic Co levels from 0.0035 mg/kg to 0.11 mg/kg in wet tissue. Moreover, prostate tissue Co contents showed large variations among individuals, but sources of the variation remain unknown. For example, the most powerful factor was age when it was found that the prostatic Co level of young adults was 2–3 times lower than that of men aged 61–87 years. It is, therefore, reasonable to assume from data of our study that inaccuracy of analytical technologies employed caused so great variability of published means for prostatic Co levels. This conclusion was supported the fact that the Certified Reference Materials for quality control of results were not used in studies reported in the 1960s[29,30,44] and in 2005.[31] 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 1207 "normal" controls were investigated from all 23 studies. As such, it is hard to draw definite conclusions about the reference value of the Co content in "normal" prostate as well as about the clinical value of the Co levels in "normal" prostates as a biomarker.

CONCLUSIONS

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

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