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REVIEW ARTICLE

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

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Abstract

A proposal has been made that prostatic strontium (Sr) content determinations may be useful in the prostate condition estimation and especially as an indicator of prostate carcinoma risk. Here we analyze data published concerning Sr prostatic levels in healthy subjects. All 2056 items in the literature of the years dating back to 1921 were identified in the following databases: PubMed, the Cochrane Library, Scopus, Web of Science, and ELSEVIER-EMBASE. The objective analysis was carried out on the data from the 26 studies, including 1453 subjects. It was found that the range of means of prostatic Sr content reported in the literature for "normal" gland widely varies from 0.16 mg/kg to <1.10 mg/kg with a median of means 0.398 mg/kg on a wet mass basis. The data encompassed a wide range of values and the sample was small, hence further studies should be performed.

Keywords: Strontium, Human prostate, Normal prostatic tissue, Biomarkers

1 | INTRODUCTION

The prostate gland is subject to various disorders and among 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.

The significant involvement of trace elements (TEs) in the function of the prostate has been shown before (4–15). It was also shown that levels of TEs in prostatic tissue, including strontium (Sr), can play a significant role in the etiology of PCa (16–20). Moreover, it was demonstrated that the changes of

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some TE levels and Zn/Sr ratios in prostate tissue can be used as biomarkers (21–27).

It was indicated low levels of Sr in human prostatic tissue (0.24 mg/kg of wet tissue) in studies published more than 60 years ago (28). Their findings revealed that the prostate gland accumulates Sr, because the level of metal in prostates was almost an order of magnitude higher than the Sr concentrations in whole blood and blood serum (29–31) and comparable to the metal level in the liver (32). Furthermore, experimental data identified that Sr compounds should be considered as potential genotoxic carcinogens (33). Moreover, several epidemiological studies revealed the association of elevated environmental Sr levels with an increased risk of esophageal carcinoma (34, 35). These findings promoted more detailed studies of the Sr content of prostatic tissue of healthy subjects, as well as of patients with different prostatic diseases, including BPH and PCa.

The impacts of TEs, including Sr, are related to their concentration. Recorded observations range from a deficiency state, through normal function as biologically essential components, to an imbalance, when an excess of one element interferes with the function of another, refer to pharmacologically active concentrations, and finally to toxic and even life-threatening concentrations (36–38). In this context, for example, a low dose of Sr has some useful effects on health (39, 40), but significant exposure to this metal and its compounds may result in adverse health effects in different organs or tissues, including malignancy (33–35, 41). However, it remains unclear what precise mechanism is responsible for Sr genotoxicity (33).

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

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

2 | 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 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 to 2020, using the key-words: prostatic trace elements, prostatic Sr content, prostatic tissue, and their combinations. For example, the search terms for Sr content were: "Sr mass fraction", "Sr content", "Sr level", "prostatic tissue Sr" and "Sr 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. Besides, references from the chosen articles were investigated as further search instruments. Relevant studies noted for each selected article were also examined for inclusion.

Eligibility Criteria

Inclusion Criteria

Only papers with quantitative data of Sr 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 Sr levels were measured in samples of prostatic tissue.

Exclusion Criteria

Studies would be excluded if they were case reports. Studies containing subjects that used Sr supplementation (Sr ranelate or citrate), or were Sr occupational exposed, as well as persons from Sr contaminated area were also excluded.

Data E xtraction

The data were extracted in a standard way, and the following available variables were extracted from each paper: method of Sr determination, number and ages of healthy persons, sample preparation, mean and median of Sr levels, standard deviations of the mean, and range of Sr 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 Sr levels in prostatic tissue. The articles were analyzed and "Median of Means" and "Range of Means" were used to examine the heterogeneity of Sr contents. The objective analysis was carried out on data from the 26 studies, with 1453 subjects.

3 | RESULTS

Information about Sr levels in prostatic tissue in various 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 (26, 27, 36). Thus, it dictates a need for reliable values of the Sr levels in the prostatic tissue of apparently healthy subjects, ranging from young adult males to elderly persons.

TABLE 1: Referencedata of Sr mass fractions (mg/kg of wet tissue) in ``normal'' human prostatictissue

Reference	Method	n	Age, range years	Sample preparation	Sr	
					M±SD	Range
Sowden 1958 [28]	RNAA	8	Adult	D, A	0.24	-
Zakutinsky et al. 1962 [42]	-	-	Adult	-	0.24	-
Tipton et al. 1963 [43]	AES	48	Adult	D, A	0.16±0.16	-
Forssen 1972 [44]	XRF	12	Adult	A, AD	<0.20-0.30	-
Schroeder et al. 1972 [45]	AES	198	Adult	D, A	0.16±0.02	-
Zaichick et al. 2010 [46]	EDXRF	10	57±11	Intact	<1.1	-
Zaichick et al. 2011 [47]	EDXRF	64	13-60	Intact	0.33±0.32	0.087-1.65
		9	13-20	Intact	0.248±0.196	-
		28	21-40	Intact	0.240±0.338	-
		27	41-60	Intact	0.444±0.522	0.44±0.52
Zaichick et al. 2012 [48]	ICPAES	64	13-60	AD	0.315±0.289	0.087-1.38
		9	13-20	AD	0.248±0.275	-
		28	21-40	AD	0.240±0.281	-
		27	41-60	AD	0.408±0.434	-
Zaichick et al. 2013 [8]	NAA+ICPAES	16	20-30	Intact, AD	0.179±0.077	-
Zaichick et al. 2014 [49]	EDXRF	37	41-87	Intact	0.425±0.357	0.162-1.65
Zaichick et al. 2014 [50]	NAA+ICPAES	28	21-40	Intact, AD	0.240±0.223	0.102-1.03
		27	41-60	Intact, AD	0.425±0.357	0.170-1.38
		10	61-87	Intact, AD	0.405±0.262	0.15-0.78
Zaichick et al. 2014 [10]	EDXRF	29	0-13	Intact	0.42±0.30	-
		21	14-30	Intact	0.24±0.12	-
		50	0-30	Intact	0.33±0.24	-
Zaichick et al. 2014 [12]	NAA+ICPAES	50	0-30	Intact, AD	0.30±0.24	-
		29	0-13	Intact, AD	0.40±0.30	-
		21	14-30	Intact, AD	0.22±0.11	-
Zaichick et al. 2014 [14]	3 Methods	16	20-30	Intact, AD	0.179±0.077	-
Zaichick et al. 2015 [51]	EDXRF	32	44-87	Intact	0.425±0.357	0.162-1.65
Zaichick et al. 2015 [52]	NAA	32	44-87	Intact	<0.51	-
Zaichick 2015 [53]	3 Methods	65	21-87	Intact, AD	0.345±0.306	-
Rossmann et al. 2016 [54]	EDXRF	37	41-79	Intact	0.425±0.357	0.162-1.65
Zaichick et al. 2016 [55]	EDXRF	37	41-79	Intact	0.425±0.357	0.162-1.65
Zaichick et al. 2016 [56]	NAA+ICPAES	28	21-40	Intact, AD	0.278±0.344	-
		27	41-60	Intact, AD	0.515±0.707	-
		10	61-87	Intact, AD	0.477±0.342	-
		37	41-87	Intact, AD	0.504±0.608	-
		65	21-87	Intact, AD	0.413±0.426	-
Zaichick et al. 2016 [57]	NAA+ICPAES	37	41-87	Intact, AD	0.398±0.316	0.148-1.38
Zaichick et al. 2016 [58]	NAA+ICPAES	32	44-87	Intact, AD	0.405±0.320	0.148-1.38
Zaichick et al. 2016 [59]	NAA+ICPAES	37	41-87	Intact, AD	0.398±0.316	0.148-1.38
Zaichick et al. 2017 [60]	3 Methods	37	41-87	Intact, AD	0.51±0.51	0.164-2.55
Zaichick 2017 [61]	3 Methods	37	41-87	Intact, AD	0.420±0.337	0.148-1.51
Zaichick et al. 2019 [62]	3 Methods	37	41-87	Intact, AD	0.420±0.337	0.148-1.51
Median of means				0.398		
Range of means (M_{min} - M_{max}), Ratio M_{max}/M_{min}				0.16 – <1.10 (<1.10/0.16) = <6.88		
All references				26		

M – arithmetic mean, SD – standard deviation of mean, Med. – Median,

RNAA – radiochemical neutron activation analysis, AES – atomic emission spectrometry, XRF – X-ray fluorescence analysis, EDXRF – energy dispersive X-ray fluorescence analysis, ICPAES – inductively coupled plasma atomic emission spectrometry, NAA-instrumental neutron activation analysis, 3 Meth-ods – EDXR+NAA+ICPAES,

D – drying at high temperature, A – ashing, AD –acid digestion

Possible publications relevant to the keywords were retrieved and screened. A total of 2056 publications were primarily obtained, of which 2030 irrelevant papers were excluded. Thus, 26 studies were ulti-mately selected according to eligibility criteria that investigated Sr levels in tissue of normal prostates (Table 1) and these 26 papers (8, 10, 12, 14, 28, 42– 62) comprised the material on which the review was

based. Many values for Sr 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% (63–66) and ash – 1% (on a wet mass basis) contents in normal prostates of adult men (43, 65, 67, 68).

ummarizes general data from the26 studies. The retrieved studies involved 1453 subjects. The ages of subjects were available for 21 studies and ranged from 0–87 years. Information about the analytical method and sample preparation used was available for 25 studies. One study determined Sr levels by radiochemical neutron activation analysis (RNAA), one – by X-ray fluorescence analysis (XRF), one – by instrumental neutron activation analysis (NAA), one – by by inductively coupled plasma atomic emission spectrometry (ICPAES), two – by atomic emission spectrometry (AES), seven - by energy dispersive X-ray fluorescence analysis (EDXRF), seven - by NAA combined with ICPAES, and in five studies 3 different methods were used – EDXRF, NAA, and ICPAES (Table 1).

Figure 1 illustrates the data set of Sr measurements in 26 studies during the period from 1958 to 2020.

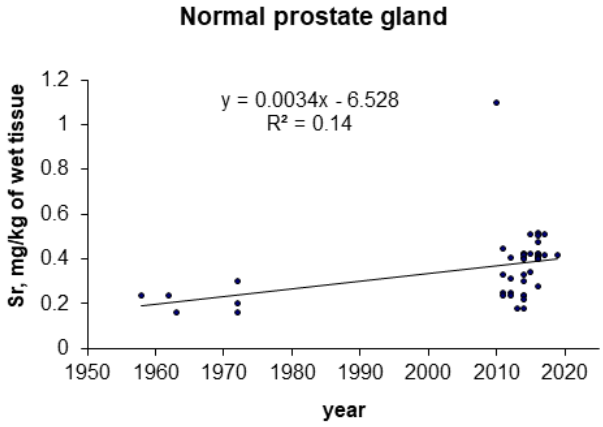

FIGURE 1: Data on Sr content in normal prostate tissue reported from 1958 to 2020.

4 | DISCUSSION

The range of means of Sr mass fractions reported in the literature for "normal" prostatic tissue varies widely from 0.16 mg/kg (43) to <1.10 mg/kg (42) with a median of means 0.398 mg/kg of wet tissue (Table 1). This variability of reported mean values can be explained a priori by a dependence of Sr content on many factors, including analytical method imperfections, differences in "normal" prostate definitions, possible non-homogeneous distribution of Sr levels throughout the prostate gland volume, age, ethnicity, diet, smoking, alcohol intake, consuming supplemental trace elements, 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 Sr content was measured in pieces of the prostate. Therefore, published data allowed us to estimate the effect of only some different factors on Sr content in "normal" prostate tissue.

Analytical M ethod

The trend line of Sr content data in "normal" prostate (Figure 1) showed that an improvement of analytical technologies during the last 50 years did not significantly impact the mean and variability of reported values. In our opinion, the leading cause of inter-observer variability was an insufficient sensitivity of analytical techniques and a lack of quality control of results in old studies published in the 50-70s.

In some reported papers such destructive analytical method as AES and ICP-AES were used. These methods require ashing and 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 (36, 69, 70). On the other hand, the Sr content of chemicals used for acid digestion can contaminate the prostate samples. Hence, when using destructive analytical methods, it is essential 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 the addition of some chemicals. It is possible to avoid these problems by using non-destructive methods, such as EDXRF, which allow to the quantification of Sr content in "normal" prostate without acid digestion. Moreover, a good agreement between results obtained by both EDXRF and ICPAES methods under a strong quality control (14, 53, 60–62) showed that in the case of Sr it is possible to avoid uncertainties connected with acid digestion. It is, therefore, reasonable to conclude that the quality control of results is a very important factor for using the Sr content in prostatic tissue as biomarkers.

Age

In a few studies, a significant increase in Sr content with increasing of age was shown by the comparison of different age groups or the Pearson's coefficient of correlation between age and Sr content in prostate tissue (47, 48, 50, 56). The most detailed investigations of age-dependence of prostatic Sr were done by Zaichick and Zaichick (56). For example, a strongly pronounced tendency for an age-related increase of Sr mass fraction was observed in the prostate for the third to sixth decades (56). In prostates of 41-60 year old men, the mean Sr mass fraction was almost 2 times higher than that in the prostates of 21-40 year old males. Thus, the accumulated information, studied by us from reported data, allowed a conclusion that there is a significant increase in Sr mass fraction in "normal" prostate from age 21 years to the sixth decade.

Androgen-independence of Prostatic Sr Levels

There was no significant difference between Sr levels in prostates of teenagers before puberty and of post-pubertal teenagers and young adults (10, 12). These findings allowed us to conclude that the Sr content in "normal" prostates does not depend on the level of androgens, and vice versa. However, studies on the association between the Sr content in "normal" prostates and the level of androgens in blood were not found.

SrIntake

The general population can be exposed to low levels of Sr primarily through consumption of food and ingestion of drinking water and to a lesser degree through inhalation of ambient air (39). The Sr content in the food is determined by the Sr level in soil which depends on the geological origin of the soil-forming rocks and anthropogenic emissions (39). In many countries there are Sr–calcium sub-regions of the biosphere and biogeochemical provinces with elevated levels of Sr in soil and disturbed Ca/Sr ratio (71).

On average, in Europe, the Sr intake of people with mixed diets amounted to 1.9-2.2 mg/day person (39, 72, 73). The most important sources are dairy products, vegetables and fruits (39, 72, 73). The highest concentration of Sr came out in nuts (73).

The habitat takes a significant effect on the Sr intake via the Sr content in the local drinking water (39). The concentration of Sr in different water types such as tap water, household wells, groundwater, and surface waters (rivers, lakes, and oceans) variate very widely (34, 74–77). However, a health reference level (HRL) for Sr 1.5 mg/L in drinking water was established, supported by an updated assessment from the Environmental Protection Agency (EPA) Office of Water (77).

Because Sr naturally occurs in the earth's crust, it is released into the atmosphere as a result of natural processes such as entrainment of dust particles, resuspension of soil by wind, and sea spray. Coastal regions have higher concentrations of Sr due to sea spray. Human activities, including milling and processing of strontium compounds, burning of coal, land application of phosphate fertilizers, and using pyrotechnic devices, release strontium into the atmosphere (78). The effect of these activities is illustrated by the deposition rates of Sr measured in peat cores of northern Indiana. The deposition has increased by a factor of 7 from 8.1 mg Sr/m^2/year in presettlement times (1339–1656) to 57.0 mg Sr/ m^2/year between 1970 and 1973 [79].

Sr is sometimes included in medications and over-the-counter dietary supplements (Sr ranelate or citrate).

Sr Content in Body Fluids, Tissues and Organs

It is well known that Sr is accumulated primarily in bone (79–81). Among soft tissues of the human body

the pancreas and liver is the major site of deposition for Sr (82). There is a correlation between this metal level in bone, whole blood and soft tissues (82). The median of prostatic Sr content means obtained in the present review (0.398 mg/kg of wet tissue) is the order of magnitude higher than the Sr concentrations in whole blood and blood serum (29–31) and comparable to the metal level in the liver (32). Thus, we can conclude that the prostate is also a target organ for Sr.

All natural chemical elements of the Periodic System, including Sr, are present in all subjects of the biosphere (36, 83, 84). During the long evolutional period intakes of Sr in organisms were more or less stable and organisms were adopted for such environmental conditions (36, 39). The situation with using Sr began to change after the industrial revolution, particularly, over the last 100-150 years.

Because of Sr extreme reactivity both to oxygen and water, this metal is not found in nature in its metallic form, but there are many different Sr minerals. Among them it is only economically viable to extract Sr from celestite (strontium sulfate - $SrSO_4$) and strontianite (strontium carbonate - $SrCO_3$). The first large-scale application of Sr was in the food industry for the production of sugar from sugar beet by a crystallization process using Sr hydroxide. The process was used well into the early part of the last century particularly in Germany where the sugar industry used 100,000 to 150,000 tons of Sr hydroxide per year. In the second part of the 20^{th} century, Sr began to use for the production cathode ray tube color TV screens. Now Sr and Sr compounds are used extensively in the manufacture of glass and ferrite ceramic magnets that are commonly exploited in such applications as crafts, holding-magnet systems, loudspeakers, magnetic couplings, magnetic therapy, motors, novelties, sensors, and toys. Sr compounds are also used to make ceramic glazes and glass to impart both strength and hardness to them. About 30% of produced Sr compounds are employed in pyrotechnics and signals. As a pure metal, Sr is used as an additive to aluminum and magnesium alloys to improve their machinability. Fluorescent lights employ phosphors using Sr magnesium phosphate and calcium Sr phosphate. Sr chromate is used as rust- and corrosion-resistant pigment in paints, varnishes and oil colors. Sr ranelate is used in the treatment of osteoporosis to reduce the risk of bone fracture in patients suffering from the disease. Moreover, Sr-containing bioactive classes are currently used as implantable materials for the management of various types of bone disorders and diseases (85). Sr titanate ($SrTiO_3$) can be a very good substrate for semiconductors and high-temperature superconductors production in the nearest future (86).

Besides stable isotopes, there are two radionuclides of Sr - ^{89}Sr and ^{90}Sr that are used in the treatment of certain types of cancer and bone metastasis from cancer (87–89). The most common radionuclide ^{90}Sr is formed in nuclear reactors or during the explosion of nuclear weapons. The radionuclide ^{90}Sr generates high-energy beta particles and has a half-life of 28 years. Hence, it is employed in systems for nuclear auxiliary power devices, which find potential applications in remote weather stations, space vehicles, navigational buoys, etc (90).

Thus, inorganic Sr is ubiquitously distributed in the environment and food, water, and air everywhere contain this element. In addition to the abundant natural sources of Sr, there are a large number of industrial sources of Sr to the soil (through atmospheric emissions originating from residues from coal, oil, and gas combustion, urban refuse, Sr mine tailings, smelter slag, waste), water (through irrigation and industrial liquid waste, and wastewater sludge application), and air (coal combustion and to a lesser extent by cement plants and/or smelters, road traffic, and fireworks) contamination (91).

Sr is an important product in the world economy. The global market for Sr estimated at 274.8 thousand tons in the year 2020, is projected to reach a revised size of 340.9 thousand tons by 2027 (91). The top three producers of Sr are China, Spain, and Mexico (92). Since the use of Sr is linked to the rapidly developing modern technology, we can assume that over the years, the need for the industry in this metal has increased significantly and would continue to increase in the future.

Exposure to high levels of stable Sr can result in impaired bone growth in children (90). Many studies found a correlation between the accumulation of Sr in bone and the presence of osteomalacia (41). An-

imal studies demonstrated that high doses of strontium induced alterations of mineralization and, in a rat model of chronic renal failure (41). Furthermore, some stable Sr compounds are cytotoxic, genotoxic, and can produce cancer (33–35, 41). Precise molecular mechanisms by which this metal causes healthy cells to transform to malignant states have yet to be fully defined (33). High levels of ^{90}Sr can damage bone marrow, cause anemia, and prevent the blood from clotting properly (90). Leukemia and cancers of the bone, nose, lung, and skin have also been seen in laboratory animals. The International Agency for Research on Cancer (IARC) has determined that ^{90}Sr is a human carcinogen (90).

Thus, according to our study for unpolluted areas no information could explain the variability of published means for "normal" prostatic Sr levels from 0.16 mg/kg to <1.10 mg/kg of wet tissue. Moreover, prostate tissue Sr contents showed large variations among individuals, but sources of the variation remain also unknown. It is, therefore, reasonable to assume from the data of our study that inaccuracy of analytical technologies employed caused so great variability of published means for prostatic Sr levels. This conclusion has supported the fact that the Certified Reference Materials for quality control of results were not used in old studies.

There are some limitations in our study, which need to be paid attention to when interpreting the results of this review. The sample size of each study was sometimes relatively small (from 8 to 65), and a total of 1453 "normal" prostates were investigated from all 26 studies. As such, it is hard to draw definite conclusions about the reference value of the Sr content in the "normal" prostate as well as about the clinical value of the Sr levels in "normal" prostates as a biomarker.

5 | CONCLUSION

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

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