Review Article

Vanadium Content of the Normal Human Prostate Gland: A Systematic Review

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Abstract

Human prostate gland is subject to various disorders. The etiology and pathogenesis of these diseases are not still well comprehended. Furthermore, despite technological developments, the differential diagnosis of prostate disorders has become progressively more intricate and argumentative. It is proposed that the vanadium (V) extent in prostatic tissue has a significant role in prostatic carcinogenesis and its measurement can be helpful as a cancer biomarker. These suggestions promoted more detailed studies of the V content in the prostatic tissue of healthy subjects. By systematic analysis of the published data for V content, this study analyzed the prostatic tissue of "normal" glands. This evaluation reviewed 2127 studies, all of which were published in the years from 1921 to 2020, and was 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 investigate the heterogeneity of the measured V content in prostates of apparently healthy men. The objective analysis was performed on data from the 17 studies, which included 664 subjects. It was found that the range of means of prostatic V content reported in the literature for "normal" gland differs widely from <0.010 mg/kg to 7.0 mg/kg with a median of means <0.034 mg/kg on a wet mass basis. Because of the small sample size and high data heterogeneity, we recommend that other primary studies are performed.

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

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 [1-4], the etiology and pathogenesis of these diseases are not still well comprehended. A better understanding of the etiology and causative risk factors is essential for the primary prevention of these diseases [5].

In our former researches, the significant involvement of Trace Elements (TEs) in the function of the prostate was found [6-17]. It was also shown that levels of TEs in prostatic tissue can play a significant role in the etiology of PCa [18-22]. Moreover, it was demonstrated that the changes of some TE levels and TE content ratios in prostate tissue can be used as biomarkers [23-29].

Low levels of V in human prostatic tissue was indicated (<0.01 mg/kg of wet tissue) in studies published almost 60 years ago [30, 31]. However, twenty years ago Banas *et al*. [32] found that the V mass fraction in the human prostate is almost three orders of magnitude higher than previously published results (7.0 mg/kg of wet tissue). This finding made the inference that the prostate gland accumulates V because the level of metal in the prostate was approximately four orders of magnitude higher the blood serum level (0.0001-0.001 mg/L) and more than two orders of magnitude higher the liver level (0.005-0.020 mg/kg of wet tissue) of the Reference Man [33]. Besides, experimental and clinical data identified that V should be considered as genotoxic carcinogens [22, 34-37]. According to the International Agency for Research on Cancer (IARC) V compound (V_2O_5) is possibly carcinogenic in humans and has been classified as a group 2B carcinogen [38]. These findings promoted more detailed studies of the V content of prostatic tissue of healthy subjects, as well as of patients with various prostatic diseases, such as BPH and PCa.

The effects of TEs, including V, are related to their concentration [39-41]. In this context, a low dose of V is an essential nutrient for humans and animals, because V complexes are cofactors for several enzymes [35]. However significant V exposure may result in adverse health effects in different organs or tissues, including malignancy such as cancers of the lung and pancreatic ductal adenocarcinoma

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[22, 37].

By now, exceedingly scant literature exists on quantitative V content in the tissue of "normal" and affected glands. The present study addresses the significance of V levels in prostatic tissue as a biomarker of the gland's condition. Hence, we systematically studied all the available relevant literature and carried out a statistical analysis of V content in the 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 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 keywords: prostatic trace elements, prostatic V content, prostatic tissue, and their combinations. For example, the search terms for V content were: "V mass fraction", "V content", "V level", "prostatic tissue V" and "V 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. Also, references from the selected articles were examined as further search tools. Relevant studies noted for each selected article were also evaluated for inclusion.

Eligibility Criteria

Inclusion Criteria

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

Exclusion Criteria

Studies were excluded if they were case reports. Studies involving subjects that were using V supplementation or V occupational exposure, as well as persons from V contaminated areas were also excluded.

Data Extraction

A standard extraction of data was applied, and the following available variables were extracted from each paper: method of V determination, number and ages of healthy persons, sample preparation, mean and median of V levels, standard deviations of the mean, and range of V 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 according to means of V levels in prostatic tissue. The articles were analyzed and "Median of Means" and "Range of Means" were used to examine the heterogeneity of V contents. The objective analysis was performed on data from the 17 studies, with 664 subjects.

Results and Discussion

Possible publications relevant to the keywords were retrieved and screened. A total of 2127 publications were primarily obtained, from which 2110 irrelevant papers were excluded. Thus, 17 studies were ultimately selected according to eligibility criteria that investigated V levels in the tissue of "normal" prostates **(Table 1)**, and these 17 papers [10, 14, 16, 30-32, 42-52] comprised the material on which the review was based. Many values for Vmass 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% [53-56] and ash – 1% (on a wet mass basis) contents in "normal" prostates of adult men [31, 55, 57, 58].

Table 1. Reference Data of V Mass Fractions (mg/kg wet tissue) in "Normal" Human Prostatic Tissue

Reference	Method	n	Age, Years Range	Sample Preparation	V, mg/kg of Wet Tissue	
					M±SD	Range
Zakutinsky *et al*.1962 [30]	-	-	Adult	-	<0.01	-
Tipton *et al*. 1963 [31]	AES	50	Adult	D, A	<0.01Med	<0.01-0.01
Banas *et al*. 2001 [32]	SRIXE	5	Adult	CS, NB	**7.0±2.0**	-
Kwiatek *et al*. 2005 [42]	SRIXE	1	Adult	CS, NB	**4.1**	-
Zaichick *et al*. 2012 [43]	ICP-AES	64	13-60	AD	≤0.037	≤0.034-0.068
Zaichick *et al*. 2013 [10]	ICP-AES	16	20-30	AD	≤0.036	≤0.034-0.068
Zaichick *et al*. 2014 [44]	ICP-AES	28	21-40	AD	<0.034	-
		27	41-60	AD	<0.034	-
		10	61-87	AD	<0.034	-
Zaichick *et al*. 2014 [14]	ICP-AES	16	20-30	AD	≤0.036	≤0.034-0.068
Zaichick *et al*. 2014 [16]	ICP-AES	50	0-30	AD	≤0.036	≤0.034-0.068
		29	0-13	AD	≤0.036	-

		21	14-30	AD	≤0.036	-
Zaichick 2015 [45]	ICP-AES	65	21-87	AD	≤0.037	≤0.034-0.068
Zaichick *et al*. 2016 [46]	ICP-AES	28	21-40	AD	<0.034	-
		27	41-60	AD	<0.034	-
		10	61-87	AD	<0.034	-
Zaichick *et al*. 2016 [47]	ICP-AES	37	41-87	AD	<0.034	-
Zaichick *et al*. 2016 [48]	ICP-AES	32	44-87	AD	<0.034	-
Zaichick *et al*. 2016 [49]	ICP-AES	37	41-87	AD	<0.034	-
Zaichick *et al*. 2017 [50]	ICP-AES	37	41-87	AD	<0.034	-
Zaichick 2017 [51]	ICP-AES	37	41-87	AD	<0.034	-
Zaichick *et al*. 2019 [52]	ICP-AES	37	41-87	AD	<0.034	-
Median of means			<0.034 or <0.034 (without 4.1 and 7.0)			
Range of means (M_{min} - M_{max}),			<0.01 -7.0 or <0.01 - ≤0.037 (without 4.1 and 7.0)			
All references			17			

M – arithmetic mean, SD – standard deviation of mean, Med - median
AES – atomic emission spectrometry, SRIXE – synchrotron radiation-induced X-ray emission, ICP-AES – inductively coupled plasma atomic emission spectrometry;
D – drying at high temperature, A – ashing, AD – acid digestion, , CS – cut section on a cryomicrotome, NB – needle biopsy.

Table 1 summarizes general data from the 17 studies. The retrieved studies involved 664 subjects. The ages of subjects were available for 13 studies and ranged from 0–87 years. Information about the analytical method and sample preparation used was available for 16 studies.

The range of means of V mass fractions reported in the literature for "normal" prostatic tissue varies widely from <0.01 mg/kg [30, 31] to 7.0 mg/kg [32] with median of means <0.034 mg/kg of wet tissue **(Table 1)**. Some maximal values of mean V mass fraction reported 4.1 mg/kg [42] and 7.0 [32] were at least two orders of magnitude higher than the median (<0.034 mg/kg of wet tissue) and can be excluded. In the study of Tipton *et al*. [31], V content was investigated in 50 prostate glands and a range of individual results was presented (<0.01 – 0.01 mg/kg of wet tissue). It means that the maximal individual content of V was 0.01 mg/kg of wet tissue.

In some studies, the content of V was quantified in a few samples, because the level of this element in all other investigated prostates was under detection limit (DL) [10, 14, 16, 43, 45]. In these studies, the possible upper limit of the mean (≤M) for V was calculated as the average mass fraction, using the value of DL instead of the individual value when these latter were found below the DL. From the presented ranges of individual results in these studies, it follows that the maximal individual content of V was 0.068 mg/kg of wet tissue.

This variability of reported means (<0.01–7.0 mg/kg of wet tissue) can be explained by a dependence of V content on many factors, including analytical method imperfections, differences in "normal" prostate definitions, possible non-homogeneous distribution of V levels throughout the prostate gland volume, age, ethnicity, diet, smoking, alcohol intake, consuming supplemental Zn and Se, and others. Not all these factors were strictly controlled in the cited studies. Furthermore, the very short list of published data and insufficient detection limit of used methods do not allow us to estimate the effect of these factors on V content in "normal" prostate tissue.

In our opinion, the leading cause of inter-observer V content variability was insufficient quality control of results in published studies. In all reported papers such destructive analytical methods as Atomic Emission Spectrometry (AES), Synchrotron Radiation-induced X-ray Emission (SRIXE), and Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES) were used. Some of these methods require ashing (AES) or acid digestion of the samples at a high temperature (ICP-AES). There is evidence that the use of this treatment causes some quantities of TEs to be lost [39, 59, 60]. On the other hand, the V content of chemicals used for acid digestion can contaminate the prostate samples. It is possible to avoid these problems by using non-destructive methods, but up to now, there are no analytical methods that allow quantifying V content in "normal" prostate without acid digestion of the samples at a high temperature. It is, therefore, reasonable to conclude that the quality control of results is a very important factor for using the V content in prostatic tissue as biomarkers. This conclusion has supported by the fact that the Certified Reference Materials for quality control of results were used only in a very few reported studies.

AAll-natural chemical elements of the Periodic System, including V, are present in all subjects of the biosphere [39, 61, 62]. During the long evolutional period intakes of V in organisms were more or less stable and organisms were adopted for such environmental conditions. Moreover, organisms involved low doses of this element in their functions [35, 63, 64]. The situation began to change after the industrial revolution, particularly, over the last 100 years.

V has a very wide area of applications. The primary use of V is in the metallurgical industry for the production of steel and non-ferrous alloys [65]. V-containing steel is widely used as spring steel, tool steel, and high-speed steel. It was also well

suited for the production of weapons. Non-iron alloys containing V are also used in space and aircraft technology, jet engines, machine parts, automobile components, as well as in the nuclear power industry. V compounds are used as an electrolyte in "vanadium redox flow batteries" [66]. V is commonly used in many other industries, especially in glass, paint, ceramic, photographic, chemical, electrochemical, and refining industries [67, 68].

Since the end of the 19th century, V was used as a panacea for various diseases, including diabetes, although its real therapeutic potential has only recently become clear [69]. V compounds are also used in medicine for treating low blood sugar content, high cholesterol level, heart disease, tuberculosis, syphilis, anemia, water retention, cancer prevention, and diseases caused by parasites [69-73]. Furthermore, over the last decades the use of titanium-aluminum-V alloy in cementless hip prostheses, has created an entirely new source of internal V exposure [74-76].

Thus, inorganic V is ubiquitously distributed in the environment, and food, water, and air everywhere contain this element. In addition to the abundant natural sources of V, there are a large number of industrial sources of V to the soil (through atmospheric emissions originating from residues from coal, oil, and gas combustion, metallurgical industry, chemical plants, oil refineries, urban refuse, mine tailings, smelter slag, and combustion of municipal waste, including pharmaceutical waste), water (through irrigation and industrial liquid waste, livestock dips, and wastewater sludge application), and air (see above) contamination. From the polluted environment, V is subsequently introduced into the food chain [65]. Thus, the risk of poisoning with V is constantly growing due to its extensive release of this element into the environment by human activity [65].

The general population can be exposed to low levels of V primarily through consumption of food and ingestion of drinking water and to a lesser degree through inhalation of ambient air [70]. V presence in food ranges from 0.001 to 0.030 mg per kg of food [77]. The main food sources of V are rice, oats, buckwheat, wheat, barley, soy, beans, peas, potatoes, mushrooms, radishes, spinach, lettuce, parsley, olives, black pepper, dill weed, mussels, crabs, beer, wine, and artificially sweetened drinks [64, 65, 70, 77]. With its physiological duality, V is essential in trace amounts (<0.0026 mg/L(kg) and toxic in excess (> 0.051 mg/L(kg) [78]. The mean V content in the diet was reported to be 0.032 mg/kg (range 0.019-0.050 mg/kg). A safe amount of V intake is less than 1.8 mg per day [70]. The typical daily dose consumed by humans is estimated to be 0.020 mg/day, although it depends on the diet and, for example, the range of daily dose ingested by the U.S. population is wider (0.010-0.060 mg/day) [70, 79, 80], the concentration of V in drinking-water depends significantly on geographical location and may range from about 0.0002 to more than 0.140 mg/L, but typical values appear to be between 0.001 and 0.006 mg/L [80, 81]. Some European states, including Italy, have established for V in drinking water a health reference value which does not exceed 0.140 mg/L, but V concentration in drinking water of some areas of an Italian volcanic region was higher than this level [81]. However, based on the health protective concentration calculated, the Office of Environmental Health Hazard Assessment recommends and supports a Notification Level of 0.015 mg/L for V in drinking water [82]. This level, representing 0.030 mg/day from consumption of 2 L/day of tap water, will be comparable with the estimated daily intake from food (see above).

Because V 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. Currently, the ambient air levels of V are quite low and vary from tenths of nanograms to a few nanograms in cubic meter [80]. In the air of big cities, the V concentration is significantly higher than in rural areas. For example, in four Belgian cities, the annual average was between 41 and 179 ng/m3 [83]. Maximum concentrations of V as high as 2000 ng/m3 occur in areas of greatest population density, during the coldest part of the year and the late evening hours [80]. It was estimated that the daily intake by inhalation is about 0.0015 mg in an urban area and 0.0002 mg in a rural area [80]. It is suspected that air V concentrations will increase in the future as a function of accelerated fossil-fuel combustion in power plants and community-heating systems.

V is sometimes included in vitamin supplements (typical intake 0.010 mg/day) [82] and oral supplementation for glycaemic control in type 2 diabetes (doze 30–150 mg daily) [71]. V compound (vanadyl sulfate) is a common supplement used to enhance weight training in athletes at doses up to 60 mg/d [70]. Thus, daily oral V supplementation in athletes and diabetic people is approximately three orders of magnitude higher than the intake from food and drinking water and can significantly increase V level in the prostate.

Contact with skin is probably a minor route of V absorption in man [80].

The total content of V in the body of adults is about 0.10−0.20 mg [84, 85]. Half of this amount is located in bones, which are the major storage pool for long-term V accumulation. Among soft tissues of the human body principal organs of V retention are the liver, kidneys, testicles, and spleen [80]. Byrne and Kosta reported concentrations of 0.0075, 0.0033, and 0.0005 mg/kg of wet tissue in the one sample of human liver, kidney, and muscle, respectively [86]. Their result for the human liver is inside the range for V contents in the liver of the Reference Man (0.005-0.020 mg/kg of wet tissue) [33]. Reported V levels in whole blood of healthy donors 0.000023-0.000108 mg/L [69] are below data for Reference Man (0.0001-0.0005 mg/kg of wet tissue) [33]. In some published studies the maximal V content of prostates was estimated to be 0.068 mg/kg of wet tissue [10, 14, 16, 43, 45].

This result is almost one order of magnitude higher than the liver level obtained by Byrne and Kosta [86] and more than 3 times higher than the maximal V level for the liver of Reference Man [33]. Using these data, we can conclude that the prostate is also a target organ for V. Published data showed an increase in V level for the tissue of the human body with age [80].

In 2013 China, South Africa, and Russia mined more than 97% of the 79,000 tons of produced V [80]. It was estimated that around 65 000 tons of V annually enter the environment from natural sources (crustal weathering and volcanic emissions) and around 200 000 tons as a result of man's activities [80]. Since the use of V 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. Published data showed an increase in V level for fluids and tissue of the human body as the V intake increased [22, 69, 80]. Thus, we can conclude that the human body burden of V, including prostate tissue, has increased over the last 100 years due to an increase in global environmental V pollution [80]. This tendency will likely continue.

The documented impact of exposure to V dust is upper respiratory tract irritation characterized by rhinitis, wheezing, nasal hemorrhage, conjunctivitis, cough, sore throat, chest pain, and asthma [70]. Ingestion of V by humans may cause respiratory dysfunction, hematologic and biochemical alterations, renal toxicity, reproductive and developmental toxicity, immunotoxicity, neurotoxicity, mutagenicity, and malignancy (potentially including PCa) [77]. However, precise molecular mechanisms by which this metal causes healthy cells to transform to malignant states have yet to be fully defined [37].

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 664 "normal" prostates were investigated from all 17 studies. As such, it is hard to draw definite conclusions about the reference value of the V content in a "normal" prostate as well as about the clinical value of the V levels in "normal" prostates as a biomarker.

Conclusion

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

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