Urol Res (1983) 11:285–290

Urological Research
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Renal Cadmium Content in the West of Scotland

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Accepted: March 23, 1983

Summary. The trace element content of kidneys has been documented in very few international centres. Significant differences can be demonstrated between the cortical and medullary levels of calcium, zinc and cadmium. For the West of Scotland the values for the latter are similar to those found in Scandinavia. There are significantly higher cadmium contents in subjects who smoke and who have evidence of ischaemic heart disease.

Key words: Trace metals, Cadmium, Kidney cortex, Ischaemic heart disease, Medulla.

Introduction

It has become possible in fairly recent times to measure the cadmium content in individual organs such as the liver and kidney by in vivo neutron activation analyses, thereby making it possible to assess the effects of cadmium exposure on work forces [4, 5].

There is, however, still a necessity to assess the cadmium content of organs such as the kidney by chemical measurements and to correlate such measurable cadmium with the cause of death. It is possible by such relatively simple methods to study much larger numbers of specimens and also to separate the cortical and medullary cadmium contents. It is also possible with good baseline data to compare the cadmium content between different areas of one country and also between countries.

The present work was undertaken in order to establish the renal cadmium content in the West of Scotland and to establish a baseline against which other areas of the UK could be compared

Method

At post mortems undertaken in Glasgow Royal Infirmary the lower pole of the left kidney was removed and stored in a plastic bag at −20 °C. When sufficient numbers of specimens were obtained they were delivered to the technician for analyses. The cortex and medulla were separated using plastic instruments and the zinc and cadmium contents of the specimens were measured in the trace metal laboratory at the Royal Infirmary. In addition, the calcium content was measured. All measurements were expressed as μg/gram of renal substance both dry and wet weight measurements. Samples were stained and prepared for light microscopy after staining with haemotoxylin eosin and by a Masson stain.

Physio-Pathological Data

The age and sex of the subjects was carefully recorded and a careful search was made to discover the cause of death along with the smoking habits of the individual. The post mortem reports were carefully studied and categorised into 7 main groups according to which disease was most likely to have been present during the patient's life, i.e. when exposure to cadmium could have been relevant to any disease process such as respiratory disorders. If a subject had died from septicaemia following a surgical procedure but who had good evidence of having had chronic emphysema then the death for purposes of assessment in terms of exposure to cadmium would be classified as pulmonary. A number of diseases such as rheumatoid arthritis was classified as miscellaneous conditions provided it was clear that the disease process had been present for some time during the patient's life. What this means is that chronic disease processes would be more likely to be affected by cadmium as compared with acute causes of death. Thus 7 broad categories of disease were established (Table 2).

Results

The results are expressed with respect to the wet weight of cadmium in renal cortex and medulla. When the first 300 kidneys had been analysed it was possible to have paired analyses for all 3 elements in 290 samples. The other 10 samples are accounted for by 5 control specimens and 5 in which results for all 3 elements were not available (Table 1).

It was found that there were highly significant differences ($p < 0.001$) for all 3 elements when cortical values were compared with medullary values.

Table 1. All disease categories – mean values Cadmium : Zinc : Calcium

	Both sexes		Males		Females	
	No.	x̄	No.	x̄	No.	x̄
Cadmium (cortex)	293	17.93	155	17.87	135	18.14
Cadmium (medulla)	290	11.51	153	11.38	135	11.79
Zinc (cortex)	293	37.68	155	35.40	135	39.35
Zinc (medulla)	290	29.81	153	28.13	135	31.75
Calcium (cortex)	293	189.20	155	210.42	135	163.05
Calcium (medulla)	290	222.88	153	247.31	135	195.67

(Cortex vs. medulla $p < 0.001$ for all 3 elements)

Table 2. x̄ cadmium μg/G wet weight – Cortex

Disease category	Both sexes		Males		Females	
	No.	x̄ Cd	No.	x̄ Cd	No.	x̄ Cd
Pulmonary	34	20.05	22	19.22	12	21.56
Cancer	108	17.95	56	16.73	52	19.27
Ischaemic heart disease	45	16.10	30	17.13	15	14.06
Hepatic disease	23	21.60	12	25.70	11	17.12
Renal disease	6	15.28	1	11.00	5	16.14
Cerebrovascular accident	30	19.27	17	14.09	13	25.00
Miscellaneous	44	16.05	17	19.03	27	14.18

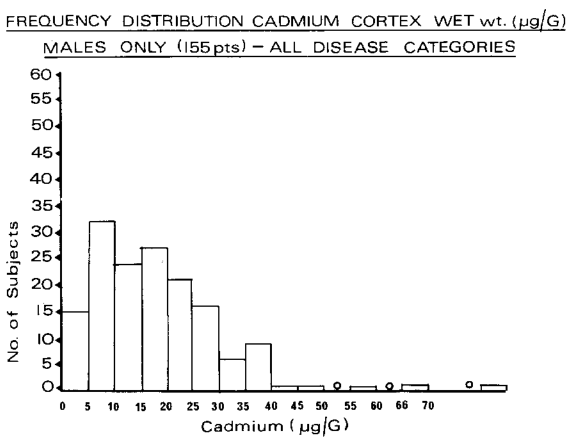

Fig. 1.

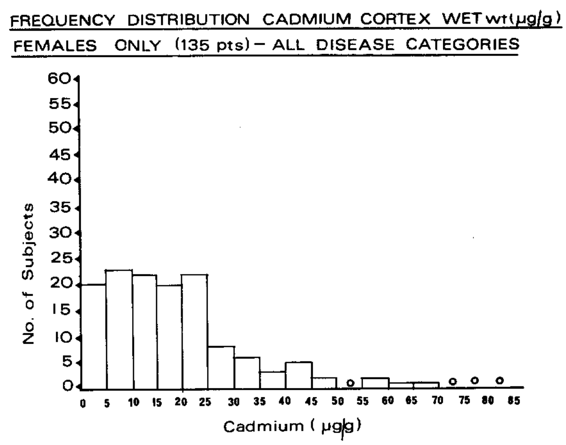

Fig. 2.

Cadmium Content vs. Disease Category

When the cortical cadmium values were analysed for each of the 7 disease categories (Table 2) no significant difference could be found when "normal distribution" analyses techniques were applied in the analysis of the results. In male (Fig. 1) and in female subjects (Fig. 2) the distribution of cadmium tended, as would be expected, to be asymmetrical. Because of this obvious analytical problem all results were analysed using a Mann Whitney test. This confirmed that there was a significant difference of both medullary cadmium and zinc values between those deaths classified as pulmonary or cancer when compared with the miscellaneous group of deaths. Also there was a significant difference of zinc content when the pulmonary death subjects were compared with the miscellaneous group (Table 3).

Effect of Age on Cadmium Content

It is usually stated that with increasing age the cadmium content of kidneys rises from a zero value at birth to reach a

Table 3. Significant differences (cadmium and zinc)

Element	Site	Significant Difference (Disease)
Cadmium	Medulla	Pulmonary vs. Miscellaneous Cancer vs. Miscellaneous
Zinc	Medulla	Pulmonary vs. Miscellaneous

maximum at age 50. In the present series the highest median values were found in the age group 31–40 (Table 4). This is a rather surprising finding. Examination of the data of the 9 subjects in the group confirmed that they did not appear to be grossly different from the general series although interestingly 2 of the subjects had hepatic disease (Table 5). Apart from this slight variation from other reported series, the general trend in our series was for the maximum levels to be found around the age of 50.

Table 4. Renal cortex/medulla cadmium $\mu g/g$ wet weight – age effect

Age Group	No.	Cortex		No.	Medulla	
		Median	Mean		Median	Mean
11–20	3	1.50	1.53	3	1.00	1.13
21–30	2	5.55	5.55	2	3.50	3.60
31–40	9	27.59	26.30	9	9.40	21.33
41–50	27	14.60	16.65	26	6.75	9.14
51–60	56	18.30	20.43	56	10.35	14.33
61–70	86	16.95	20.32	85	12.00	13.09
71–80	79	15.50	16.77	79	9.50	9.94
81+	28	8.95	10.75	28	5.85	6.90

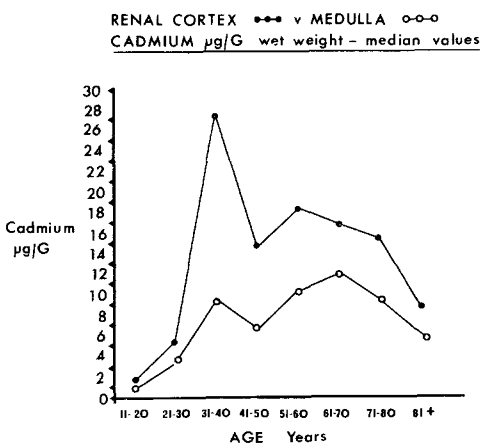

Fig. 3

After the age of 50 there was a fall in cortical cadmium but the medullary cadmium only really started to fall after age 60 (Fig. 3). Statistical analysis was applied (Mann Whitney test) to ascertain whether or not there was any obvious variation between age groups. The greatest differences were found when subjects over the age of 81 were compared with those in younger age groups. With respect to cadmium and zinc the greatest differences were found between those subjects who were more than 50 years old when compared with those over 81 years of age. With calcium there was the same pattern of very highly significant differences with respect to those over 50 years of age but a decade earlier, i.e. over 40 years, there were highly significant differences for the element when compared with those over 81.

Table 5. Renal cortical/medullary cadmium (Subjects aged 31–40)

Sex	Age	Disease	Cadmium $\mu g/G$	
			Cortex	Medulla
Male	31	Marfans syndrome	23.6	5.2
Male	36	Cirrhosis	45.0	70.0
Male	40	Ischaemic heart disease	27.5	11.0
Female	32	Peritonitis	3.6	3.0
Female	33	Partial hepatectomy	3.4	2.5
Female	33	Renal failure	9.2	9.2
Female	35	Ca cervix	19.1	9.4
Female	39	Broncho pneumonia	40.8	38.7
Female	40	Emphysema	59.5	43.4

Table 6. Age band 81 and over; significant differences with other age bands

Element	Site	Age band	Significance
Cadmium	Cortex	51–60	a
		61–70	a
		71–80	b
Cadmium	Medulla	51–60	b
		61–70	b
Zinc	Cortex	51–60	a
		61–70	b
		71–80	c
Zinc	Medulla	51–60	b
		61–70	b
Calcium	Cortex	41–50	b
		51–60	a
		61–70	a
Calcium	Medulla	41–50	b
		51–60	a
		61–70	a

Difference: a very highly significant
b highly significant
c significant

Smoking Habits

Renal cortical cadmium is known to be affected by smoking and as far as possible efforts were made to determine the smoking habits of the individual subjects. In 195 subjects sufficient information was available to allow a correlation between cadmium content and smoking habits to be assessed (Table 7).

Table 7. Smokers vs non smokers. Cadmium/zinc content wet weight (renal cortex)

Element	Site	Daily cigarette consumption		
		Less than 10	10–25	25+
Cadmium	Cortex	–	c	a
Cadmium	Medulla	–	c	b
Zinc	Medulla	*	–	–

[a] significant
[b] highly significant
[c] very highly significant

When non-smokers were compared with those who smoke any cigarettes to amounts in excess of 25 per day, then the cadmium or zinc contents became statistically significantly different (Table 7). Non-smokers had significantly less cadmium than smokers but surprisingly it was in those subjects who smoked between 10–25 cigarettes where the greatest differences were found as compared with even heavier smokers. It is recognized that most persons will regularly underestimate their total daily consumption of cigarettes. No differences with respect to calcium could be found in any group comparison.

Having ascertained the smoking habits of the individuals it was possible to group these individuals into 4 main disease categories (Table 8).

By classifying those subjects dying from the carcinoma of lung and gastrointestinal cancers it was possible to consider 4 groups of at least 30 subjects. Comparison of median values confirmed that there was a significant difference

Table 8. Cadmium – smokers vs non smokers

Disease	Total	Missing Information	Smokers		Non smokers	
	No.	No.	No.	$\bar{x}$	No.	$\bar{x}$
Pulmonary	34	7	17	19.80	10	18.20
Ischaemic heart disease	45	15	19	19.80	11	12.60
Ca lung	30	8	16	17.60	6	15.60
Ca gastrointestinal tract	42	12	13	20.70	17	19.50

$\bar{x}$ = median value

Table 9. Cadmium content of kidneys – reported series

Study	Year	No.	Age	Cadmium cortex
Elinder et al. (6)	1976	292	50	22.00 μg/G
Miller et al. (13)	1976	91	0.5	16.80 μg/G
Tuschiya et al. (18)	1976	160	40–49	203.8 μg/G
Present	1981	155	(males)	17.87 μg/G
		135	(females)	18.14 μg/G

($p < 0.05$) (Mann Whitney test) between the group of smokers dying from ischaemic heart disease as compared with the non smokers dying from similar causes (Table 8) with respect to cortical cadmium content.

Comparison With Other Centres

Three other major series have been completed in studies similar to the present (Table 9). The most major difference is in the Japanese series where the overall mean cadmium is 57.99 μg/G tissue.

Discussion

At birth human beings do not have a measurable cadmium content in their kidneys but with increasing age the cadmium content in the body in general and the kidney in particular steadily increases.

Like other metals [2] it is possible that the intake of cadmium can be affected because the individual lives in close proximity to a major production site. However, very few people live in such a unique environment and cadmium intake from the diet is much more likely to account for the general levels found in population groups. In most countries something in the order of 25–75 μg/day are absorbed from food sources [8].

Man can increase the amount of potential cadmium in the diet by manipulating the environment. For example, by adding fertilizers, including sewage sludge, to soil, then the cadmium uptake by plants can be greatly enhanced [1]. Atmospheric pollution is another potential source of human contamination by cadmium. Some authors have shown a positive correlation between atmospheric cadmium levels and death rates from hypertension [3], but such observations thus far have not been substantiated.

By whatever route cadmium enters the body it eventually is concentrated in the kidney. From studies of such accumulations of cadmium it has been shown in the experimental animal that there is a positive correlation between renal cadmium levels and the development of hypertension in such animals [17]. If such a relationship is proven, it could have very important implications with respect to hypertension in humans, especially among smokers. It is recognized that renal cadmium values are higher in men than in women and that smokers have higher cadmium levels than non smokers [9] and that cigarette smoking probably contributes 0.1 to 0.2 μg of cadmium per cigarette [16].

Various attempts have been made to correlate the cause of death to the renal content of cadmium. One of the most interesting aspects has been attempts to relate cadmium contents to cancer in general and to specific tumours in particular. It has been recorded that there is a significantly higher renal content of cadmium in the kidney in those dying from bronchogenic carcinoma [15] and similarly in renal cancer [12].

Care has to be taken in the interpretation of cadmium content and disease, however, as it has been shown that in neoplasia there may be a wide variation in tissue cadmium levels particularly where individuals actually succumb to cancer [14].

In the assessment of metallic poisons and their effects on the population in general, there has been relatively little study, and therefore accurate information is probably lacking [7]. By contrast there is now a greater awareness of the effects of industrial exposure and possible carcinogenic effects [11].

The present study has enabled the level of cadmium in the kidney to be established in a sample of 300 post mortem kidneys obtained in one unit in the West of Scotland. Apart from this basic and necessary data it has emphasised the significant differences between the cortex and medulla with respect to cadmium, zinc and calcium contents. In the case of calcium this is an inverse relationship.

When compared with other series, the values found in this area are similar to those found in other western countries such as Sweden [6] and Australia [13]. In subjects from all three of these countries the cadmium levels are more than half as much as the levels found in Japanese studies [2]. What is of interest, however, is that in one age band – 40–49 in the Japanese series – the levels found are at the "critical concentration" values [10].

The present study has confirmed that smoking can be a very important factor in adding to the renal concentration of cadmium.

Of particular interest in the context of cadmium content is the finding of statistically significantly higher levels in those dying from pulmonary or neoplastic causes as compared with those in the miscellaneous group.

Of further interest and rather unexpected is the significant difference between smokers and non-smokers in those dying from ischaemic heart disease. In an area with a recognised high death rate from coronary heart disease this observation clearly merits further study and consideration.

Conclusions

The cadmium, zinc and calcium levels have been measured in 290 human kidneys. Cortical versus medullary levels have been found to be significantly different for all three elements and interestingly statistically different levels have been found in cancer and pulmonary disease. In addition those who died of ischaemic heart disease and who smoked had significantly higher renal cadmium values.

Acknowledgement. This research was carried out under contract with the Department of the Environment, whose permission to publish this paper has been obtained. We are very grateful to the Department of Pathology, Glasgow Royal Infirmary, for the supply of specimens.

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