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Analysis of features of accumulation and distribution of heavy metals in kidney tissue of patients with kidney cell cancer

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SUMMARY

The content of heavy metals by spectrophotometric method (nickel, copper, manganese, cadmium, zinc, lead, chromium and iron) in the renal cortex of 15 patients who underwent nephrectomy for kidney cancer was studied. Residents of Dnipropetrovsk region were conditionally divided into two groups, depending on the place of residence. The study group included residents of industrial cities and surrounding areas, and the control group – conditionally included residents of Tsarychansky district, the ecological situation in which is considered relatively prosperous. The mean age of the patients in whom kidney tissue was taken for the study was 54.75±11.43 years. Four patients were active smokers. Analysis of the content of heavy metals in the renal cortex of patients with kidney cancer revealed that the levels of copper, cadmium, zinc and lead were higher in residents of the intensive industrial zone compared to residents of the control group. But the high reliability of this difference was found only for cadmium. A study of the content of heavy metals in the renal cortex depending on the age of patients showed a tendency to the significance of differences between age groups in cadmium content and, to a lesser extent, in manganese and zinc content. Comparison of cadmium content in the cortical substance of the kidneys of active smokers and non-smokers found that in active smokers the concentration of cadmium in the cortical substance of the kidneys was significantly higher. The research revealed the peculiarities of the accumulation of heavy metals in patients with kidney cancer depending on the place of residence, age and smoking in the anamnesis of residents of the intensive industrial region of Dnipropetrovsk region, which require further in-depth study.

INTRODUCTION
Вступ

Heavy metal ions occupy one of the leading places among man-made pollutants, which even in microdoses can cause dangerous damage to sensitive anatomical and physiological systems and the development of pathological conditions. Heavy metal ions are characterized by high toxicity and biochemical activity, which allows them to be classified as ecocidal and biocidal xenobiotics. The most common way of entering the components of ecological systems and ultimately into the human body are industrial emissions into reservoirs and their accumulation in surface and groundwater, in addition to possible acute and chronic intoxication with heavy metal ions in industrial conditions [6, 8].

Human tissues with food receive up to 70% of the total amount of heavy metal ions that pollute the internal environment, the body. Thus, according to Rondia D., 1989, 26–62% of Cd, 45–52% of Pb, 21–31% of Cu, 22–37% of Mn pass from the soil to vegetables [27]. The parameters to be monitored by the Joint FAO and WHO Food Code Commission include mercury, cadmium, lead, copper, arsenic, zinc and iron in foods. In the future, heavy metals, according to forecasts and estimates of some researchers, may become more dangerous than waste from nuclear power plants, even come out on top or share it with pesticides [3].

People are rarely exposed to just one toxic element in the workplace or in the environment. It is usually a combination of toxic metals. There is a growing need for further study of the nephrotoxicity of metal combinations, as normal cellular responses change when exposed to metal combinations that reflect realistic exposure situations in habitats and the environment.

The aim of our study was to study the content of heavy metals in the renal cortex of patients undergoing nephrectomy for kidney cancer, as our previous studies [4, 5, 9] showed that the amount of heavy metals in the soils of Dnepropetrovsk region, as well as in blood and urine of workers of enterprises and residents of Dnipropetrovsk region significantly exceeds normal values.

MATERIALS AND METHODS
Матеріали і методи дослідження

We studied the content of heavy metals (nickel, copper, manganese, cadmium, zinc, lead, chromium and iron) in the cortical substance of the kidneys of 15 residents of Dnipropetrovsk region by spectrophotometric method. Kidney tissue for the study was obtained from patients who underwent nephrectomy for kidney cancer. The cortical area of the kidney was removed from the opposite edge of the kidney, which was not affected by the tumor. Depending on the place of residence, the residents of the region were conditionally divided into two groups. Residents of industrial cities and surrounding areas were assigned to the study group, and residents of Tsarychansky district, where the environmental situation is considered relatively favorable, were conditionally assigned to the control group.

Studies of heavy metals were performed on an atomic absorption spectrophotometer AAS-1 N "Carl Zeiss" (Germany), using a hot mixture of propane-butane-air or acetylene-air for atomization. Measurements of the concentration of heavy metals in the cortical substance of the kidneys were performed in the mode of absorption at a certain wavelength. The concentration of the trace element in the samples was determined by the following formula:

$$C_0 = \frac{C_1 \times V \times 1000}{P},$$

where C_0 – concentration (mg/kg) in the samples; C_1 – concentration in solution (mg/l); V is the volume of the solution; P – weight of the sample in mg; 1000 – conversion factor.

To determine the content of heavy metals by the atomic absorption method, a sample of kidney tissue was prepared, which consisted of the following. The kidney tissue was crushed, weighed on analytical scales, subjected to drying in an oven at t=100–110 °C. After drying, the sample was weighed again and recorded the result (for further calculations). The dried sample was placed in a porcelain crucible and subjected to dry ashing in a muffle furnace, raising the temperature every hour by 50 °C to a constant t=470 °C Ashing was carried out until complete combustion of organic matter (resulting in light gray ash).

Further treatment of the sample consisted of wet ashing with concentrated nitric acid (CHA): the sample was dissolved in 2 cm^3 HNO3 conc. when heated in a sand bath. The sample was then filtered, adjusted to the mark with 10 cm^3 of double-distilled water. The obtained filtrate was investigated on an atomic absorption spectrophotometer [7].

Metal concentrations in μg/ml were determined by plotting the readings of the instrument (extinction) and known metal concentrations in standard solutions. To convert from μg/ml to mg/kg, the formula is used:

$$C = X * V / m,$$

where C – metal concentration, mg/kg; X is the concentration of the metal on the calibrated graph,

μg/ml; V – sample volume, ml; m is the weight of the sample in terms of dry matter, g.

The obtained indicators are translated into concentration indicators for the weight of wet matter (kidneys) by the formula:

$$C_{vol} = C / k,$$

where C_{vol} – concentration of metal in the moist cortical substance of the kidney, mg/kg; C – concentration of metal in the dry crust of the kidney, mg/kg; k is the coefficient of humidity.

To assess the significance of differences between the studied samples, given their relatively small size, and also given that the study was conducted on biological objects, the following nonparametric methods were chosen: B – Mana–Whitney test (MW), Kolmogorov test – Smirnov (KS) and the Wald–Wolfowitz test (WW). The significance of differences between the control and experimental groups was assessed in parallel with these three methods. Median test and Kruskall–Wallis ANOVA allow to estimate differences between several samples at the same time (more than 2). These criteria were used to compare differences in metal content by three age groups of patients [2].

RESULTS AND DISCUSSION
Результати та їх обговорення

The age of patients who underwent nephrectomy for kidney cancer and who had kidney tissue taken for examination ranged from 40 to 77 years. The mean age of the patients in whom kidney tissue was taken for the study was 54.75±11.43 years. Four patients were active smokers. Analysis of the content of heavy metals in the renal cortex of patients with renal cell carcinoma revealed that the levels of copper, cadmium, zinc and lead were higher in residents of the intensive industrial zone compared to residents of the control group. But the high reliability of this difference was found only for cadmium (Table 1). Nickel was detected in only one patient at a concentration of 0.2081 mg/kg, and chromium in the renal cortex was not detected.

It has long been known that exposure to cadmium can lead to various types of ill health, including nephropathy, lung disease, impaired calcium metabolism and disorders of the skeletal system [17]. Cadmium affects the metabolism of a number of trace elements, primarily zinc, copper, iron and selenium. The effect of cadmium depends on its interaction with zinc (Zn). Cadmium is able to replace zinc in chelates of this metal and to predominate in this respect all the latter metals, due to the similar structure of the atoms of both elements and the similarity of the tetrahedral complexes formed by them [1]. Cadmium can be considered, therefore, as a specific antimetabolite of zinc and some other essential trace elements. Prolonged or chronic exposure to cadmium makes the kidneys the main target of toxic damage [28]. When exposed to cadmium, renal disorders are as follows: low molecular weight proteinuria, aminoaciduria, glucosuria and necrosis of cells of the proximal renal tubules. The main role in the toxicity of cadmium is played by metallothionein (MT), a low molecular weight, cysteine-rich protein weighing 6500 daltons. MT is responsible for the regulation and maintenance of the body's necessary metals zinc and copper, and MT can play the role of scavenger of free radicals [18]. Studies have shown high affinity for Cd in MT, as well as the fact that cadmium can replace zinc in metallothionein upon entry into the cell. MT synthesis is also induced by levels of zinc, copper and cadmium. The main factor determining the occurrence of nephrotoxicity may be the balance between free cadmium and CdMT in renal tissue [28].

TABLE 1. The content of heavy metals in the cortical substance of the kidneys of patients with kidney cancer (mg/kg)

Metal	Research group		Control group		Assessment of credibility (p)			
	M	m	M	m	t-criterion	W-W	M-W	K-S
Ni	0,00	0,00	0,21	0,00	–	1,000	1,000	–
Cu	3,02	3,05	1,80	0,94	0,514	0,293	0,564	p = n.s.
Mn	0,48	0,21	0,45	0,20	0,805	0,293	0,885	p = n.s.
Cd	16,39	21,87	1,90	1,05	0,285	0,001	0,009	p < .05
Zn	10,29	13,39	9,65	7,28	0,939	0,293	0,564	p = n.s.
Pb	1,07	0,22	0,00	0,00	–	1,000	1,000	–
Cr	0,00	0,00	0,00	0,00	–	1,000	1,000	–
Fe	24,70	13,04	24,00	0,00	0,962	1,000	1,000	–

Note: n.s. – error > 5%.

The amount of cadmium accumulated in the body increases with age [24], so we conducted a study of the content of heavy metals in the cortex of the kidneys, depending on the age of patients. Patients from the study group were divided into three subgroups by age. Patients aged 40 to 49 years were included in the first subgroup, from 50 to 59 years – in the second, and in the third subgroup – from 60 and older. The average content of cadmium in the renal cortex in patients of the 1st subgroup was 3.87946±0.672026 mg/kg, in patients of the 2nd – 13.2765±14.62290 mg/kg and in patients of the 3rd subgroup – 26.3953±30.04762 mg/kg (Table 2). Thus, the content of cadmium in the cortical substance of the kidneys, according to our data, also increases with age. There is a tendency to the significance of differences between age groups in cadmium content and, to a lesser extent, in manganese and zinc content. To unequivocally assess these trends, studies with enlarged samples are needed.

Under chronic exposure, cadmium is captured and accumulated in hepatocytes as a CdMT complex, and this complex is released into the blood as a result of transformations of hepatocytes or their toxic damage. Low molecular weight CdMT is filtered through the glomerular membrane and reabsorbed in segments S1 and S2 of the proximal tubules by the mechanisms of normal reabsorption of proteins. Nephrotoxicity develops when cadmium ions are released into the cytosol after the destruction of CdMT in lysosomes and when there is a supersaturation of renal MT [29].

The development of cadmium nephropathy or tubular tubular dysfunction is also possible in persons who are not directly involved in production, but live near enterprises [19, 25]. Therefore, it is important to know the critical concentration of cadmium in the kidney tissue when the first symptoms of the disease develop. According to the WHO, such a critical concentration in the cortical layer of the kidneys of humans is a concentration of cadmium not exceeding 200 μg/g of kidney tissue. There may be no tubular dysfunction at Cd levels of 300 to 400 μg/g [26]. Studies in Belgium and the United States have shown that when the concentration of cadmium in the cortical layer of the kidneys reaches 200 mg/kg, signs of renal dysfunction (increased excretion of İ2-microglobulin and microalbuminuria) appear in 10% of people in contact with this metal [11, 16].

We also compared the cadmium content in the renal cortex of kidney cancer patients in active smokers and non-smokers and found that the cadmium content in the renal cortex in non-smokers was 4.54±1.40 mg/kg, and in active smokers – 28.25±26.70 mg/kg. That is, in active smokers with kidney cancer, the concentration of cadmium in the cortical substance of the kidneys was significantly higher. It should be noted that all active smokers were men, worked in enterprises, ie a significant accumulation of cadmium in the crust was associated with their main job.

A study of the concentration of heavy metals in a biopsy of the cortical substance of the kidneys, selected from 36 healthy Swedish donors, showed that the concentration of cadmium in the cortical substance of the kidneys is higher in active smokers compared to non-smokers [10].

The content of lead in the renal cortex of the study group of patients according to our study was 1.07±0.22 mg/kg and ranged from 1.45 mg/kg to

TABLE 2. The content of heavy metals in the cortical substance of the kidneys of patients with kidney cancer, depending on age

Age group	Heavy metals(mg/kg)							
	Ni	Cu	Mn	Cd	Zn	Pb	Cr	Fe
Age 40–49	0	1,63283± 0,733165	0,3851± 0,139969	3,87946± 0,672026	3,877± 1,256444	0,34426± 0,596287	0	6,1966± #/0
Age 50–59	0	2,00475± 0,831024	0,57327± 0,120988	13,2765± 14,62290	21,4267± 19,78019	0,59652± 0,719599	0	37,9317± 12,68429
Age 60–77	0	4,66646± 4,34328	0,4723± 0,298088	26,3953± 30,04762	5,23116± 3,488902	0,64433± 0,565988	0	22,7102± 7,080551
Median test	p=1	p=0,7659	p=0,4646	p=0,1225	p=0,4646	p=0,6592	p=1	p=0,1396
Kruskall–Wallis ANOVA	p=1	p=0,3211	p=0,2623	p=0,1963	p=0,3495	p=0,8187	p=1	p=0,1575
Wald–Wolfowitz	p=1	p=0,537	p=0,837	p=0,537	p=0,064	p=1	p=1	p=1
Mann–Whitney	p=1	p=0,180	p=0,456	p=0,101	p=0,655	p=1	p=1	p=1
Kolmogorov–Smirnov	p=–	p=n/d	p=n/d	p=n/d	p=n/d	p=–	p=–	p=–

0 mg/kg (Table 1). Depending on the age of the patients, the analysis of the lead content in the cortical substance of the kidneys of patients with kidney cancer also revealed a relative increase in its content with the age of the patients. Thus, the concentration of lead in patients aged 40 to 49 years was 0.34±0.59, in patients aged 50 to 59 years – 0.64±0.56 and in patients aged 60 years and older – 0.59±0.72 mg/kg (Table 2).

Lead nephropathy is characterized by mitochondrial damage and pathognomonic lead body inclusions in the cells of the renal proximal tubules [13]. A high incidence of renal adenocarcinoma has been reported among workers exposed to lead and has also been found in rodents exposed to lead with drinking water over a long period of time [15, 30]. Numerous studies and epidemiological analyzes suggest that the nephropathological effects of chronic lead exposure include tubulotoxicity, interstitial lesions, and the development of renal adenocarcinoma, and that renal lead-binding proteins may play a role in these processes [13].

Lead-binding proteins (PbBPs) are low molecular weight proteins rich in aspartate and glutamate dicarboxylated amino acids, dissociation constants in the range of 10–8 M for lead. These proteins affect the intracellular bioavailability of Pb in target organs such as the kidneys and brain [12, 28].

Pb-binding proteins may play a role in the formation of intranuclear lead cells-inclusions [23, 28]. Morphological hallmarks of chronic exposure to lead are lead inclusions, which are lead-protein aggregates in the nucleus [22]. A series of saturation and sedimentation techniques have shown that cytosolic PbBPs promote free cell transfer to the nucleus or reverse capture of lead [23]. Such studies confirm that PbBPs proteins may play an important role in the development of lead-induced renal cell carcinomas, as well as mediate known disorders in the expression of genes that are associated with chronic lead exposure. Lead causes changes in renal gene expression and tubular mitosis, which is associated with the formation of intranuclear inclusion bodies, which have been known for many years and may indirectly affect the process of carcinogenesis [14, 28]. Studies in rodent models suggest that PbBPs proteins promote lead transport to the nucleus and that this complex may bind to chromatin and interact with 5 specific prime flanking regions of the regulatory / promoter sites of those genes that detect damaged expression sequences [13, 14, 28]. This mechanism can also activate the expression of oncogenes, leading to cellular transformation and carcinogenesis [14].

Analysis of the iron content in the renal cortex of the study and control groups of patients with kidney cancer did not show a difference. Thus, the concentration of iron in the cortical substance of the kidneys of the study group was 24.70±13.04 mg/kg, and in the cortical substance of the kidneys of the control group – 24.00±0.00 mg/kg (Table 1). The concentration of copper in the renal cortex of the study group was 3.02±3.05 mg/kg, and in the control group – 1.80±0.94 mg/kg and despite the fact that in the study group the concentration was higher than in control group, this difference was insignificant.

The significance of differences using non-parametric methods between the age groups of 40–49 years and 60–77 years was assessed. The tendency to reliability of differences between age groups on the content of copper and cadmium is revealed (Table 2).

The concentration of manganese in the cortical substance of the kidneys of the study group was 0.48±0.21 mg/kg, and in the cortical substance of the kidneys of the control group – 0.45±0.20 mg/kg, ie the content of manganese in the cortical substance of both study and control groups were the same. No significant difference in zinc content was found. Thus, the content of zinc in the cortical substance of the kidneys of the studied group was 10.29±13.39 mg/kg, and in the cortical substance of the kidneys of the control group – 9.65±7.28 mg/kg.

Thus, a study of the content of heavy metals in the cortical substance of the kidneys of patients who underwent surgery for kidney cancer, showed that the highest content in the cortical substance of the kidney was iron (24.70±13.04 mg/kg), which is essential for the body. Cadmium is in second place (16.39±21.87 mg/kg) as one of the most toxic heavy metals. Despite the fact that lead is carcinogenic to the kidney, its concentration in the renal cortex of the study group was only 1.07± 0.22 mg/kg. Competitive use of cadmium, according to the literature, reduced the renal effects of lead, which was noted by lower accumulation of lead in the kidneys and the absence of intranuclear inclusion bodies [20, 21]. Thus, studies of the interactions between Pb and Cd have shown that Cd acts as an effective competitor, displacing lead from rat renal Pb-binding protein 2-microglobulin [23]. Taken together, these results suggest that cadmium may impair renal reabsorption and accumulation of lead by affecting the binding of PbBPs and Pb2 +, as well as the formation of intranuclear inclusion parts.

The research revealed the peculiarities of the accumulation of heavy metals of patients with kidney cancer depending on place of residence, age and smoking in the anamnesis of residents of the intensive industrial region of Dnipropetrovsk region, which require further in-depth study.

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РЕФЕРАТ

Аналіз особливостей накопичення та розподілу важких металів у тканині нирок хворих на нирково-клітинний рак

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Проведено вивчення вмісту важких металів спектрофотометричним методом (нікелю, міді, марганцю, кадмію, цинку, свинцю, хрому і заліза) у кірковій речовині нирок 15 хворих, яким була виконана нефректомія з приводу раку нирки. Жителі Дніпропетровської області були умовно розподілені на дві групи, у залежності від місця проживання. До досліджуваної групи були віднесені жителі індустріальних міст та прилеглих районів, а до контрольної – були умовно віднесені жителі Царичанського району, екологічна обстановка в якому вважається відносно благополучною. Середній вік пацієнтів, у яких була взята тканина нирки для дослідження, становив 54,75±11,43 року. Четверо пацієнтів були активними курцями. При аналізі вмісту важких металів у кірковій речовині нирок хворих на рак нирки виявлено, що рівень міді, кадмію, цинку та свинцю був вищим у жителів інтенсивної промислової зони у порівнянні з жителями контрольної групи. Але висока достовірність цієї різниці була виявлена тільки для кадмію. Дослідження вмісту важких металів у кірковій речовині нирок у залежності від віку пацієнтів виявило тенденцію до достовірності різниць між віковими групами по вмісту кадмію і, меншою мірою, по вмісту марганцю і цинку. Порівняння вмісту кадмію в кірковій речовині нирок у активних курців та некурців виявило, що у актив-

РЕФЕРАТ

Анализ особенностей накопления и распределения тяжелых металлов в ткани почек больных почечно-клеточным раком

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Проведено изучение содержания тяжелых металлов спектрофотометрическим методом (никеля, меди, марганца, кадмия, цинка, свинца, хрома и железа) в корковом веществе почек 15 больных, которым была выполнена нефрэктомия по поводу рака почки. Жители Днепропетровской области были условно разделены на две группы, в зависимости от места жительства. В исследуемую группу были отнесены жители индустриальных городов и близлежащих районов, а в контрольную группу были условно отнесены жители Царичанского района, экологическая обстановка в котором считается относительно благополучной. Средний возраст пациентов, у которых взята ткань почки для исследования, составлял 54,75±11,43 лет. Четверо пациентов были активными курильщиками. При анализе содержания тяжелых металлов в корковом веществе почек больных раком почки выявлено, что уровень меди, кадмия, цинка и свинца был выше у жителей интенсивной промышленной зоны по сравнению с жителями контрольной группы. Но высокая достоверность этой разницы была обнаружена только для кадмия. Исследование содержания тяжелых металлов в корковом веществе почек в зависимости от возраста пациентов выявило тенденцию к достоверности разниц между возрастными группами по содержанию кадмия и, в меньшей степени, по

них курців концентрація кадмію у кірковій речовині нирок була достовірно вищою.

У результаті проведеного дослідження виявлені особливості накопичення важких металів у хворих на рак нирки в залежності від місця проживання, віку та куріння в анамнезі жителів інтенсивного промислового регіону Дніпропетровської області, які потребують подальшого поглибленого вивчення.

Ключові слова: нирково-клітинна карцинома, рак, важкі метали.

содержанию марганца и цинка. Сравнение содержания кадмия в корковом веществе почек у активных курильщиков и некурящих выявило, что у активных курильщиков концентрация кадмия в корковом веществе почек была достоверно выше.

В результате проведенного исследования выявлены особенности накопления тяжелых металлов у больных раком почки в зависимости от места жительства, возраста и курения в анамнезе жителей интенсивного промышленного региона Днепропетровской области, которые требуют дальнейшего углубленного изучения.

Ключевые слова: почечно-клеточная карцинома, рак, тяжелые металлы.