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The investigation of specific biochemical markers in monitoring kidney function of drug addicts

Badanie przydatności specyficznych wskaźników biochemicznych w ocenie funkcji nerek u osób uzależnionych od narkotyków

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E Manuscript Preparation
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Summary

Introduction: An increasingly important issue in the Polish population is drug abuse. It leads to extensive damage of parenchymal organs, including kidney. Establishing early markers of organ damage and their monitoring during rehabilitation therapy is therefore of pivotal importance. This study evaluated the utility of highly specific and selective markers (NGAL, IL-18, a and π-GST isoenzyme, and ß2-M). The influence of opioid drugs and other factors on kidney function (HIV and HCV infections, duration and the kind of drugs abused) was determined.

Materials and Methods: Urine collected from 83 subjects who abused drugs and 33 healthy volunteers was tested with ELISA using specific antibodies (IBL, Biotron, Bioporto-Diagnostics). HIV infection was confirmed with western-blotting and HCV with PCR. CD4 lymphocytes were quantified with flow cytometry. RFLP and PCR were used to determine the viral load of HIV and HCV (genotype).

Results: A significant increase of IL-18, NGAL and β2M activity in heroin addicts compared to the control group was noted as well as the influence of HIV infection on NGAL and β2M excretion. A statistically significant (p=0.04) correlation between the viral load and IL-18 concentration was noted while no significant influence of the duration and the kind of drugs abused, the route of intake or the age of addicts was seen. Only the NGAL concentration was sex dependent and significantly higher in women.

Discussion: This study showed the specific, clinical utility of IL-18, NGAL, and β2M in the evaluation of renal function in drug addicts. Early detection of nephropathy with biochemical indicators might help prevent severe conditions that require hospitalization and intensive care.

Key words: **drugs • addicted • heroin • nephropathy • kidney markers**

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Introduction

Clinical trials concentrating on the evaluation of toxic effects of narcotics are burdened with numerous difficulties, taking into account, among others, illegality of their possession and usage. Hospital Emergency Departments and Intensive Care Units often admit drug abusers in very severe general condition, which is caused by drug overdosage and impaired function of important organs responsible for elimination of endo- and exogenous substances from the body. Of special interest is their effect on the kidneys, failure of which may lead to disturbed functioning of all the organs. Available literature contains few reports on nephrotoxicity associated with sporadic or permanent usage of these substances. Such studies have been conducted mainly *in vitro* [3], although there were trials to demonstrate an association between kidney impairment and histological findings on autopsy in heroin addicted individuals [8].

Function of the excretory organ in individuals addicted to opiates may be affected by a number of factors, including individual response of the organism, applied dosage, tolerance and adverse effects caused by this group of drugs [16]. A distinct diuretic or natriuretic response is observed regardless of the route of administration. In physiological conditions the endogenous opioid receptor system does not exert any significant effect on renal excretion. On the other hand, its activation is associated with a significant effect [22].

Thus an adequate selection of indicators enabling early detection of renal function impairment is of utmost significance.

The aim of the study was to evaluate the effect of opioids use in association with other factors, such as HIV and HCV infection, kind of addiction, and duration of drug abuse on renal function.

Materials and Methods

The studies involved in total 116 individuals, including 83 subjects taking intravenous injections of heroin in the past, and 33 healthy individuals who constituted the control group. Demographic data of the addicted individuals and the control group are presented in Table 1.

Every person was informed of the aim and methods of the trial and gave informed consent to participate in the study. The study protocol was approved by the Bioethics Committee at Wrocław Medical University (No. 157/2010).

The levels and activity of renal function parameters were evaluated in urine, which was collected into polyethylene containers without any preservatives. In order to eliminate the morphotic elements, the urine was centrifuged for 15 min at 3000 rpm immediately after collecting. It was stored at -80°C until examination. Virusological studies (HIV, HCV) were performed on blood collected for clot, which was stored at 4°C until examination.

The evaluation of renal function was based on urine levels of the following parameters: IL-18 (interleukin 18), NGAL (human neutrophil gelatinase-activated lipocalin), the activity of: GST-α – alpha glutathione S-transferase isoenzyme specific for the proximal part of the renal tubules, GST-π – S-glutathione S-transferase pi characteristic for the distal part of renal tubules, collecting tubules and loop of Henle, as well as the levels of β_2M – β_2-microglobulin, a micromolecular protein.

Table 1. Demographic data of heroin addicted individuals and healthy controls

Study group	Number of subjects	Age (years)				Gender	
		$\bar{X}$	±SD	from	to	female	male
Heroin addicted individuals	83	32.20	7.30	21	51	20	53
Healthy controls	33	27.53	5.82	21	40	20	13

Table 2. Renal function parameters in heroin-addicted individuals and in healthy controls

Investigated parameter	Values of renal function parameters							
	Heroin addicted individuals				Control group			
	$\bar{X}$	±SD	from	to	$\bar{X}$	±SD	from	to
IL-18 [pg/ml]	37.42**	59.94	1.40	505.40	8.92	5.04	0.20	18.60
NGAL [ng/ml]	0.59*	1.15	0.10	8.20	0.26	0.24	0.10	1.00
GST-α [ng/ml]	6.28	12.63	0.20	75.80	2.42	2.00	0.20	7.00
GST-π [ng/ml]	11.75	31.90	0.40	280.00	6.06	3.06	1.30	15.0
β2M [ng/ml]	0.51**	1.07	0.10	9.10	0.19	0.09	0.10	0.50

Statistical significance of differences in mean values of the renal function parameters between heroin addicted individuals and healthy controls at: * p=0.04, ** p<0.001.

Table 3. Renal function parameters in heroin addicted individuals and in healthy controls in relation to urine creatinine level

Investigated parameter	Values of renal function parameters in relation to urine creatinine level							
	Heroin addicted individuals				Control group			
	$\bar{X}$	±SD	from	to	$\bar{X}$	±SD	from	to
IL-18 [pg/mg of creatinine]	30.85*	31.52	1.90	172.67	8.66	5.84	0.18	23.80
NGAL [ng/mg of creatinine]	0.50	0.87	0.03	5.71	0.27	0.24	0.04	0.96
GST-α [ng/mg of creatinine]	5.47	10.36	0.09	78.14	2.76	2.78	0.18	10.18
GST-π [ng/mg of creatinine]	12.99	43.26	0.43	392.71	6.33	3.70	0.63	14.25
β2M [ng/mg of creatinine]	0.67	1.95	0.03	16.25	0.20	0.11	0.06	0.49

Statistical significance of differences in mean IL-18 values between heroin addicted individuals and healthy controls at: * p<0.001.

The levels of IL-18, NGAL, β_2M as well GST-α, GST-π activity were measured by the immunoenzymatic ELISA method using specific antibodies (manufactured by IBL, Biotron, Bioporto-Diagnostics), while the level of creatinine was determined by means of the immunological fluorescence polarization method with a VIVA Analyzer, Siemens.

HIV and HCV infection were ruled out on the basis of negative ELISA test for antibodies, anti-HIV and p24 antigen as well as anti-HCV respectively. In order to confirm HIV infection, western blot examination was performed, while to confirm HCV the PCR method was used. The number of CD4 lymphocytes was determined by means of flow cytofluorometry. The PCR method in combination with RFLP was used to determine HIV and HCV viremia as well as HCV genotyping.

Statistical analysis of the findings was performed by means of Statistica PL 9.1 software. The Shapiro-Wilk test was used to evaluate normal distribution of all the investigated parameters. As none of the parameters, except for the urine creatinine level, revealed normal distribution, non-parametric tests had to be used: the Kolmogorov-Smirnov or the Mann-Whitney U test, depending on the size of the investigated group. Relationships between the observed parameters were analyzed by means of Spearman's linear correlation coefficient or the ANOVA rank Kruskal–Wallis test. Values p<0.05 were considered statistically significant.

Results

Mean levels of IL-18, NGAL and β_2M were statistically significant in the group of heroin addicts in comparison to controls and were: 37.42±59.94 and 8.92±5.04 pg/ml, 0.59±1.15 and 0.26±0.24 ng/ml as well as 0.51±1.07 and 0.19±0.09 ng/ml respectively. The values of the remaining parameters, despite lack of statistical significance, were also higher in individuals taking heroin in comparison to healthy subjects. Table 2 presents mean values of individual parameters of renal function for both investigated groups.

Moreover, the levels of creatinine in urine differed statistically significantly (p=0.05) in both the investigated groups and were 1.44±0.82 mg/ml (from 0.09 to 3.58 mg/ml) in heroin addicted individuals and 1.14±0.49 mg/ml (from 0.35 to 2.21 mg/ml) in healthy controls.

In order to eliminate the effect of the volume of diuresis and personal features on enzymuria, values of the parameters were calculated in relation to the urine creatinine level [14,19]. The values are presented in Table 3.

Table 4. Renal function parameters in heroin-addicted women and men

Investigated parameter	Values of renal function parameters calculated in relation to urine creatinine level							
	Women (n=20)				Men (n=63)			
	$\bar{X}$	±SD	from	to	$\bar{X}$	±SD	from	to
IL-18 [pg/mg of creatinine]	45.55	46.11	4.18	172.67	26.17	23.89	1.90	113.98
NGAL [ng/mg of creatinine]	1.02*	1.52	0.07	5.71	0.33	0.43	0.03	2.59
GST-α [ng/mg of creatinine]	5.48	9.15	0.20	34.72	5.46	10.78	0.09	78.14
GST-π [ng/mg of creatinine]	28.56	86.53	0.64	392.71	8.05	8.78	0.43	38.37
β2M [ng/mg of creatinine]	0.48	0.47	0.07	1.61	0.73	2.22	0.03	16.25

Statistical significance of differences in mean NGAL level in relation to urine creatinine level between heroin addicted women and men at: * p=0.01.

Table 5. Renal function parameters in individuals addicted to heroin and in patients with mixed type addiction.

Investigated parameter	Values of renal function parameters in relation to urine creatinine level							
	Type of addiction							
	Heroin				Mixed			
	$\bar{X}$	±SD	from	to	$\bar{X}$	±SD	from	To
IL-18 [pg/mg of creatinine]	29.64	27.28	3.67	128.79	32.68	37.43	1.90	172.67
NGAL [ng/mg of creatinine]	0.63	1.09	0.03	5.71	0.30	0.25	0.04	1.08
GST-α [ng/mg of creatinine]	5.90	12.37	0.09	78.14	4.82	6.31	0.12	27.91
GST-π [ng/mg of creatinine]	15.55	55.16	0.43	392.71	9.11	10.45	0.64	42.10
β2M [ng/mg of creatinine]	0.74	2.32	0.03	16.25	0.57	1.21	0.04	5.38

Analysis of mean values of renal function parameters after dilution of urine demonstrated only a statistically significant increase in the level of IL-18 in the group of heroin addicted subjects (30.85±31.52 pg/mg of creatinine) in comparison to the control group (8.66±5.84 pg/mg of creatinine). Values of the remaining parameters did not differ statistically significantly between the observed groups, although the values were higher in heroin addicts. A difference on the border of statistical significance (p=0.06) was demonstrated for the level of β_2M in heroin addicted subjects in comparison to healthy subjects.

No effect of age on the values of investigated parameters was demonstrated in both groups; however, a relationship was observed between the level of NGAL and gender in the group of heroin addicts. Its mean level in women (1.02±1.52 ng/mg of creatinine) was statistically significantly (p=0.01) higher in comparison to men (0.33±0.43 ng/mg of creatinine). Also, a difference on the border of statistical significance (p=0.07) was demonstrated for IL-18 level. Mean values of this renal function parameter calculated per milligram of creatinine in heroin-addicted women and men are presented in Table 4.

The group of individuals addicted to psychoactive agents is very heterogeneous – most of them sporadically took other drugs in the past, and some of them were addicted to several narcotics. Two further subgroups were separated on the basis of psychiatric assessment and ICD-10 classification: individuals addicted only to heroin (50 subjects) and individuals with mixed addiction (33 subjects). No statistically significant differences were found in the mean levels of IL-18, NGAL, GST-α, GST-π and β_2M calculated per milligram of creatinine between the above-mentioned subgroups, as presented in Table 5.

Furthermore, values of the renal function parameters calculated per milligram of creatinine were not affected by such factors as addiction period, duration of the longest bender (continued daily drug use) as well as purity of heroin. In subjects using in the past so-called compote (containing solvents used for its production: acetone, vinegar, synthetic resins) and so-called brown sugar (the most contaminated kind of heroin), the levels of investigated parameters did not differ statistically significantly. Renal function parameters in the group of heroin addicted indi-

Table 6. Renal function parameters in heroin addicts in relation to the kind of heroin taken in the past.

Parameter	Renal function parameters calculated in relation to urine creatinine level							
	Subjects taking in the past so-called							
	compote (n=39)				brown sugar (n=40)			
	$\bar{X}$	±SD	from	to	$\bar{X}$	±SD	from	to
IL-18 [pg/mg of creatinine]	27.49	27.63	1.90	128.79	34.51	35.82	3.49	172.67
NGAL [ng/mg of creatinine]	0.56	1.06	0.03	5.71	0.46	0.69	0.04	3.93
GST-α [ng/mg of creatinine]	4.70	7.90	0.09	34.72	6.64	12.69	0.12	78.14
GST-π [ng/mg of creatinine]	7.70	8.98	0.43	36.56	18.32	61.42	0.51	392.71
β2M [ng/mg of creatinine]	0.87	2.71	0.03	16.25	0.53	0.91	0.03	4.98

Table 7. Renal function parameters in subjects addicted to heroin who took or did not take cocaine in the past

Parameter	Renal function parameters calculated in relation to urine creatinine level							
	Subjects who did not take cocaine in the past				Subjects who took cocaine sporadically			
	$\bar{X}$	±SD	from	to	$\bar{X}$	±SD	from	to
IL-18 [pg/mg of creatinine]	32.27	31.42	3.67	172.67	29.17	31.98	1.90	128.79
NGAL [ng/mg of creatinine]	0.41	0.55	0.03	3.18	0.60	1.14	0.04	5.71
GST-α [ng/mg of creatinine]	4.49	5.66	0.26	26.93	6.62	14.04	0.09	78.14
GST-π [ng/mg of creatinine]	9.19	10.22	0.64	38.37	17.49	63.12	0.43	392.71
β2M [ng/mg of creatinine]	0.81	2.51	0.04	16.25	0.50	0.87	0.03	4.98

Table 8. Renal function parameters in subjects addicted to heroin who took or did not take amphetamine in the past

Parameter	Renal function parameters calculated in relation to urine creatinine level							
	Subjects who did not take amphetamine in the past				Subjects who took amphetamine sporadically			
	$\bar{X}$	±SD	from	to	$\bar{X}$	±SD	from	to
IL-18 [pg/mg of creatinine]	35.51	23.95	3.49	68.90	30.29	32.41	1.90	172.67
NGAL [ng/mg of creatinine]	0.69	1.08	0.04	3.18	0.48	0.85	0.32	5.71
GST-α [ng/mg of creatinine]	16.85	24.71	0.85	78.11	4.08	5.98	0.09	34.73
GST-π [ng/mg of creatinine]	10.22	11.61	1.23	34.77	13.33	45.67	0.43	392.71
β2M [ng/mg of creatinine]	0.35	0.38	0.08	1.33	0.71	2.06	0.03	16.25

viduals in relation to the kind of heroin taken in the past are presented in Table 6.

Cocaine and amphetamine are psychoactive substances with a proven nephrotoxic effect. In the investigated group none of the subjects was addicted to these drugs; however, in the past cocaine and amphetamine were taken sporadically by 38 and 74 patients respectively. Tables 7 and 8 present renal function parameters in subjects addicted to heroin in relation to the past usage of cocaine and amphetamine.

Concomitant occurrence of HIV and/or HCV infection is an important issue affecting the health condition of individuals addicted to psychoactive substances. The infections may additionally deteriorate their health status, as both viruses exert a nephrotoxic effect. Our studies demonstrated only the effect of HIV infection on NGAL and β_2M levels, which in subjects free from HIV infection were 0.39±0.1 ng/mg of creatinine and 0.33±0.44 ng/mg of creatinine, while in the HIV (+) group they were 0.53±0.1 ng/mg of creatinine and 1.60±3.58 ng/mg of creatinine respec-

Table 9. Renal function parameters in subjects addicted to heroin in relation to HIV infection

Parameter	Renal function parameters calculated in relation to urine creatinine level							
	Subjects free from HIV infection (n=61)				Subjects with HIV infection (n=22)			
	$\bar{X}$	±SD	from	to	$\bar{X}$	±SD	from	to
IL-18 [pg/mg of creatinine]	29.77	32.78	1.90	172.66	33.85	28.24	3.67	113.98
NGAL [ng/mg of creatinine]	0.39*	0.10	0.03	5.71	0.53	0.10	0.07	1.19
GST-α [ng/mg of creatinine]	6.24	11.85	0.12	78.14	3.32	3.34	0.09	15.0
GST-π [ng/mg of creatinine]	14.49	50.21	0.43	392.71	8.84	8.90	0.92	36.56
β2M [ng/mg of creatinine]	0.33**	0.44	0.03	2.69	1.60	3.58	0.07	16.25

Statistical significance of differences in mean renal function parameters levels between heroin addicted subjects HIV (+) and HIV (-) at: * $p<0.025$, ** $p=0.03$.

Table 10. Renal function parameters in subjects addicted to heroin in relation to HCV infection

Parameter	Renal function parameters calculated in relation to urine creatinine level							
	Subjects free from HCV infection (n=7)				Subjects with HCV infection (n=76)			
	$\bar{X}$	±SD	from	to	$\bar{X}$	±SD	from	to
IL-18 [pg/mg of creatinine]	26.34	14.65	5.19	44.54	31.27	32.67	1.90	172.67
NGAL [ng/mg of creatinine]	0.21	0.20	0.03	0.53	0.53	0.90	0.04	5.71
GST-α [ng/mg of creatinine]	6.08	7.64	0.26	17.42	5.41	10.61	0.09	78.14
GST-π [ng/mg of creatinine]	13.58	14.35	0.64	38.73	12.94	45.04	0.43	392.71
β2M [ng/mg of creatinine]	0.29	0.23	0.11	0.80	0.71	2.03	0.03	16.25

Table 11. Renal function parameters in subjects addicted to heroin in relation to HCV genotype

Parameter	Renal function parameters calculated in relation to urine creatinine level											
	Genotype											
	1 (n=16)				3 (n=23)				4 (n=6)			
	$\bar{X}$	±SD	from	to	$\bar{X}$	±SD	from	to	$\bar{X}$	±SD	from	to
L-18 [pg/mg of creatinine]	29.99	32.32	1.90	128.79	39.01	41.58	7.14	172.68	22.79	18.03	5.66	45.00
NGAL [ng/mg of creatinine]	0.23	0.20	0.07	0.85	0.80	1.39	0.08	5.71	0.44	0.41	0.07	1.19
GST-α [ng/mg of creatinine]	10.91	19.92	0.17	78.14	4.57	6.12	0.12	27.91	3.24	4.65	0.09	12.63
GST-π [ng/mg of creatinine]	8.35	6.95	0.78	21.18	25.39	80.71	0.43	392.71	3.95	1.56	2.51	6.55
β2M [ng/mg of creatinine]	0.32	0.33	0.03	1.21	0.41	0.56	0.04	2.69	0.20	0.07	0.13	0.28

tively. Tables 9 and 10 present renal function parameters in subjects addicted to heroin in relation to HIV and HCV infection respectively.

No association was found between the analyzed renal function parameters for individual genotypes and HCV viremia (Table 11).

The occurrence of renal function impairment in the course of HIV infection is significantly affected by the compromised activity of the immune system expressed by the number of CD4 lymphocytes and viremia. Analysis of obtained results indicated only a statistically significant correlation (p=0.04) between the level of IL-18 and viremia (IL-18 level = 0.13 x 10^{-3} x viremia + 26.658; r^2 = 0.21). A diagram illustrating the above relationship is presented in Fig. 1.

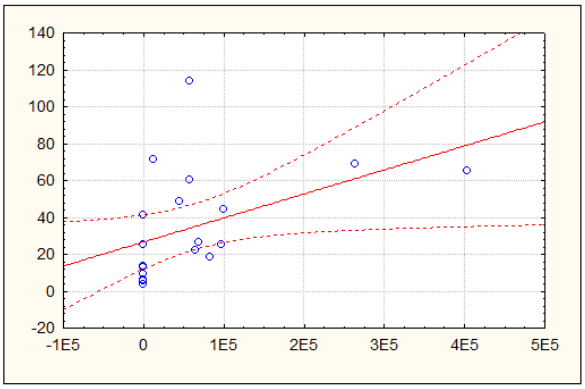

Fig. 1. Relationship between the level of IL-18 calculated per milligram of creatinine and HIV viremia

Discussion

The examinations revealed elevated levels of investigated renal function parameters (IL-18, NGAL, glutathione transferase isoenzymes α-GST, π-GST and β_2-microglobulin) in drug addicts in comparison to the control group. The levels of IL-18, NGAL and β_2M were found to be especially statistically significantly elevated in comparison to controls. The first reports suggesting a nephropathic effect of heroin were published as early as in the 1970s (HAN) [8].

High IL-18 activity may point to the mechanism of induction of the inflammatory response in the renal epithelial cells, and its constant expression may be important for the reactions of immediate damage. Data from the literature indicate that intravenous administration of heroin induces an immunological response (high level of IgM antibodies), which is a reaction to the drug itself and associated contaminations. Such a reaction was absent in the case of heroin inhalations [9,10,19]. A number of histological changes were described in persons taking heroin intravenously – numerous deposits of IgM and IgG antibodies and complement C3 were found in the kidneys [8,9,10]. Morphine also causes interactions between connective tissue cells and macrophages, both local and those present in pathological conditions. Moreover, prolonged abuse of heroin contributes to increased activity of T lymphocytes [4, 12,23].

The increased level of NGAL observed in our studies may evidence ischemic injury of the renal tubules. It seems to be induced by a potent contractile mechanism of heroin on renal blood vessels. It is believed that a combination of several drugs is burdened with higher nephrotoxicity than the use of one drug [20,21]. In the performed studies sporadic use of cocaine apart from heroin did not have any effect on renal function. On the other hand, subjects using opioids and amphetamine revealed a significantly higher level of α-GST than the group of addicted subjects not using amphetamine.

Elevated levels of GST-α in the group of drug users taking additionally amphetamine in comparison to controls may suggest that these individuals develop damage of the proximal tubules, as the GST-α isoenzyme is located mainly in the proximal tubules. Xenobiotics may destroy every segment of the nephron; however, most susceptible are the cells of the proximal tubule, as they reveal the highest metabolic activity and a very high osmotic gradient. The proximal convoluted tubule, contrarily to the distal convoluted tubule, possesses a less tight epithelial layer, and the cellular transport of the majority of xenobiotics occurs in this part of the nephron [15].

Many reports contain information on the nephrotoxic effect of amphetamine derivatives [2,5 6,14,21]. Nephrotoxicity may lead to transient injury of the renal tubules, hyponatremia, which is closely associated with increasing levels of ADH, and damage to the proximal renal tubules, which is evidenced by the GST-α increase revealed in our studies.

Elevated levels of β_2M found in addicted subjects with HIV infection in comparison to both control subjects and addicted HIV(-) subjects demonstrate that concomitant infection has a negative effect on renal function. This has been confirmed by literature data [1,11,13,17,18]. The most common renal pathology in the course of HIV infection includes focal segmental glomerulosclerosis as well as glomerular immune complex deposits. Also the inflammatory process induced by HIV presence plays an important role in kidney failure. This is confirmed by the observed association between IL-18 level and HIV viremia.

The obtained findings did not show any significant influence of the kind of heroin on renal function. However, there are reports in the literature on an association between the incidence of focal segmental glomerulosclerosis (FSGS) and purity of used heroin. It is assumed that contaminations added to heroin in order to increase the drug volume may induce an immune response and evoke inflammatory processes [7,23].

Conclusions

1. The present study proved that drug abuse exerts an unfavorable effect on renal function. Renal injury in individuals addicted to drugs has multifactorial character and is also affected by concomitant HIV infection and other substances taken simultaneously.

2. Among the investigated nephrotoxicity parameters, of special diagnostic value in the evaluation of renal function in drug abusers are IL-18, NGAL, and β_2-microglobulin.

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