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The effect of chronic alcohol abuse on liver damage and function – analysis of basic biochemical and coagulological parameters

Wpływ przewlekłego nadużywania alkoholu na czynność wątroby i stopień jej uszkodzenia – analiza podstawowych parametrów biochemicznych i koagulologicznych

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Abstract

Introduction: The aim of this study was to evaluate the effect of the duration of alcohol dependence on liver function and the degree of hepatocytes damage.

Material and methods: The study included 400 men with diagnosed alcohol dependence based

Streszczenie

Wprowadzenie: Celem niniejszego badania była ocena wpływu czasu trwania uzależnienia od alkoholu na parametry funkcji wątroby i stopień uszkodzenia hepatocytów.

Materiał i metody: Badaniem objęto 400 mężczyzn ze zdiagnozowanym uzależnieniem od alko-

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on ICD-10, and 50 non-dependent males, who formed the control group. Alcohol dependent patients were divided into 4 groups according to the duration of dependence: I (1-5 years), II (6-10), III (11-15) and IV (16-20). In all groups, serum aminotransferases, bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), total protein, albumin, prothrombin time and activated partial thromboplastin time were tested and statistically analysed.

Results: Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and GGT were positively correlated with the duration of alcohol dependence. Serum albumin and total protein were negatively correlated. A U-shaped relationship between duration of alcohol dependence and serum alkaline phosphatase (ALP) was observed.

Discussion: Alanine, aspartate, GGT, ALP and bilirubin are parameters assessing liver function. According to many studies they allow to differentiate the aetiology of liver dysfunction to alcoholic and non-alcoholic. The degree of dysfunction can be assessed on the basis of albumin concentrations and coagulation parameters.

Conclusions: The adverse effect of chronic alcohol abuse on liver function is observed even after 1-5 years of dependence. After this time the damage of hepatocytes is almost evident. After 16 years of alcohol dependence, liver function is seriously impaired, as is shown in a greatly reduced concentration of total protein and albumin. Negative alcohol effect on the liver is also seen in impaired clotting.

Keywords: Alcoholic liver disease, Aminotransferases, Coagulation parameters

holu na podstawie kryteriów ICD-10 i 50 mężczyzn nieuzależnionych, tworzących grupę kontrolną. Pacjenci uzależnieni od alkoholu zostali podzieleni na 4 grupy w zależności od czasu trwania uzależnienia: I (1–5 lat), II (6–10 lat), III (11–15 lat) i IV (16–20 lat). We wszystkich grupach badano i statystycznie analizowano aktywność aminotransferaz, bilirubiny, fosfatazy alkalicznej, gamma-glutamylotranspeptydazy (GGT), białka całkowitego, albuminy, czasu protrombinowego i czasu częściowej tromboplastyny po aktywacji.

Wyniki: Zaobserwowano dodatnią korelację między czasem trwania uzależnienia od alkoholu a aktywnością aminotransferazy asparaginianowej (AST), aminotransferazy alaninowej (ALT) i GGT. Ujemnie korelowały stężenia białka całkowitego i albumin w surowicy. Zaobserwowano także zależność między czasem trwania uzależnienia a aktywnością fosfatazy alkalicznej.

Omówienie: ALT, AST, GGT, fosfataza alkaliczna i bilirubina są parametrami oceniającymi czynność wątroby. Zgodnie z wieloma badaniami pozwalają na różnicowanie etiologii uszkodzenia wątroby na alkoholową i niealkoholową. Stopień dysfunkcji można pośrednio ocenić na podstawie stężenia albuminy i parametrów krzepnięcia.

Wnioski: Niekorzystny wpływ przewlekłego nadużywania alkoholu na czynność wątroby obserwuje się nawet po 1–5 latach uzależnienia. Po 16 latach trwania uzależnienia od alkoholu czynność wątroby jest poważnie upośledzona, o czym świadczą znacznie obniżone stężenie białka całkowitego i albumin w surowicy, a także zaburzenia układu krzepnięcia.

Słowa kluczowe: alkoholowa choroba wątroby, aminotransferazy, parametry krzepnięcia

Introduction

Alcohol is the most widely used addictive substance in the world. In Poland about 200 thousand people received out-patient treatment due to alcohol disorders every year. The number in residential treatment surpasses 75 thousand [1]. There are many more alcohol abusers as 3 million have clinical symptoms of alcohol abuse or dependence (12% of population aged 18-64) [2]. The average age of onset of alcohol use in Poland is 10-11 years and the percentage of abstainers among 15 years old is 8-10%. According to the ESPAD study, in 2015 almost half of 15-year-olds drink regularly (at least once in a month preceding the survey) and 12.5% reported intoxication in the last 30 days preceding the survey [3]. The effects of alcohol on the human body are varied and include practically all organs.

Ethanol metabolism takes place mainly in the liver, which is the organ particularly vulnerable to its damaging impact. The aim of this study was to evaluate the correlation between duration of chronic alcohol abuse and the severity of liver damage and its dysfunction. One of the main liver

functions is the production of proteins, including coagulation factors. Impaired liver function will then appear in a reduced concentration of total protein, albumin as well as impaired coagulation.

Material and methods

The study included 400 men at the age from 19 to 60 years, hospitalised at the general psychiatric wards and at the somatic-psychiatric ward in the Public Hospital for the Mentaly Ill in Rybnik, with diagnosed alcohol dependence based on ICD-10 criteria, and 50 male control group, who were not alcohol-dependent. In the study there was no division due to the type of alcohol consumed, as the patients consumed all types of alcohol. Alcohol dependent patients were divided into 4 groups according to the duration of dependence:

- I group 1-5 years of dependence – 100 men,
- II group 6-10 years – 100 men,
- III group 11-15 years – 100 men,
- IV group 16-20 years – 100 men.

Patients characteristics were presented in Table I.

In all groups serum aminotransferases: alanine (ALT) and aspartate (AST), total bilirubin (BIL-T), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total protein (TP), albumin (ALB), prothrombin time (PT) and activated partial thromboplastin time (APTT) were tested and statistically analysed. Biochemical tests: AST, ALT, ALP, GGT, BIL-T, total protein were performed on biochemical analyser Hitachi-902, using Spinreakt and Roche Diagnostics reagents. Serum albumin concentration was measured by EPOLL-20 BIO analyser on Alfa Diagnostics reagents. PT and APTT were evaluated on the Coag Chrom 3003 coagulometer (Bio-Ksel Company) by chronometric method using Bio-Mar reagent kits.

Inclusion criteria:

- patients with confirmed alcohol dependence,
- men aged 25 to 60 years,
- markers of viral hepatitis HBs-Ag negative, anti-HCV absent,
- negative unheated serum regain test for *Treponema pallidum*.

Exclusion criteria:

- hypertension,
- diabetes mellitus,
- age > 60 years, to avoid the impact of aging as well as diseases associated with old age on the parameters of the liver function.

Results

Our study showed a gradual increase of alanine and aspartate transaminases activity in all tested groups with significantly higher values in group II, III and IV compared to the control group. The percentage of patients with abnormal, increased activity of ALT was 48% in I, 76% in II, 88% in III and

Table I. Patient characteristics. Mean values were presented with standard deviations in parentheses

Factor	I	II	III	IV	Control
Duration of alcohol dependence (yr)	1-5	6-10	11-15	16-20	–
Mean age (yr)	27 (3)	38 (7)	48 (6)	55 (5)	40 (13)
Mean BMI (kg/m^2)	24.7 (2.3)	25.8 (2.9)	25.7 (3.1)	23.9 (2.7)	26.4 (2.35)
Gender – male	100.00%	100.00%	100.00%	100.00%	100.00%
% of patients with normal parameters of liver function					
ALT	52	24	12	6	99
AST	66	30	11	6	99
GGT	23	11	5	5	96
ALP	94	90	92	79	100
BIL-T	57	49	24	9	99
ALB	89	63	43	14	100
TP	98	96	94	73	100
PT	72	80	47	17	86
APTT	77	55	34	13	96

ALT – alanine aminotransferase, AST – aspartate aminotransferase, ALP – alkaline phosphatase, GGT – gamma-glutamyl transpeptidase, BIL-T – total bilirubin, ALB – albumin, TP – total protein, PT – prothrombin time, APTT – activated partial thromboplastin time

Table II. Mean values with standard deviations and percentage changes in biochemical parameters depending on the duration of alcohol dependence

Factor	I	II	III	IV	Control
	n = 100	*n* = 100	*n* = 100	*n* = 100	*n* = 50
AST [U/L]	42.91 ± 38.85 157.18% II; III; IV	87.01 ± 72.92 318.71% I; III; IV; CTR	118.89 ± 83.52 435.49% I; II; IV; CTR	165.72 ± 99.95 607.03% I; II; III; CTR	27.30 ± 5.67 100.00% II; III; IV
ALT [U/L]	43.87 ± 23.72 139.98% II; III; IV	85.99 ± 68.10 274.37% I; IV; CTR	111.00 ± 84.21 372.08% I; IV; CTR	158.98 ± 108.88 354.18% I; II; III; CTR	31.34 ± 7.51 100.00% II; III; IV
ALP [U/L]	179.04 ± 51.89 96.00% IV	174.30 ± 62.05 93.45% IV	182.51 ± 60.93 97.86% IV	215.60 ± 63.00 115.60% I; II; III; CTR	186.50 ± 20.89 100.00% IV
GGT [U/L]	56.42 ± 25.45 170.13% III; IV	100.22 ± 241.93 302.23% III; IV	197.79 ± 274.57 596.47% I; II; CTR	212.87 ± 180.85 641.94% I; II; CTR	33.16 ± 8.22 100.00% I; II
BIL-T [umol/l]	13.14 ± 8.90 139.60% II; III;IV	20.11 ± 19.43 213.58% I; III; IV; CTR	27.49 ± 18.93 291.98% I; II; IV; CTR	33.95 ± 19.41 360.63% I; II; III; CTR	9.41 ± 3.04 100.00% II; III; IV
ALB [g/dl]	3.91 ± 0.36 95.01% II; III; IV; CTR	3.50 ± 0.46 85.16% I; III; IV; CTR	3.32 ± 0.44 80.80% I; II; IV; CTR	3.11 ± 0.44 75.54% I; II; III; CTR	4.11 ± 0.35 100.00% I; II; III; IV
TP [g/dl]	7.62 ± 0.49 101.52% II; III; IV	7.28 ± 0.69 97.00% I; III; IV	6.86 ± 0.67 91.35% I; II; IV; CTR	6.34 ± 0.61 84.42% I; II; III; CTR	7.51 ± 0.48 100.00% III; IV
PT [s]	12.64 ± 1.09 104.00% II; III; IV	13.99 ± 1.88 115.08% I; III; IV; CTR	16.15 ± 2.72 132.89% I; II; IV; CTR	17.85 ± 2.38 146.88% I; II; III; CTR	12.15 ± 0.79 100.00% II; III; IV
APTT [s]	31.40 ± 3.64 102.38% II; III; IV	35.66 ± 4.24 116.28% I; III; IV; CTR	39.08 ± 8.06 127.43% I; II; IV; CTR	41.27 ± 5.92 134.58% I; II; III; CTR	30.66 ± 2.64 100.00% II; III; IV

I; II; III; IV; CTR – statistical significance comparing to group (respectively): I; II; III; IV and control (p value < 0.001)

94% in IV group. The percentage of patients with increased, abnormal activity of AST was 34% in I, 70% in II, 89% in III and 94% in IV group. De Ritis ratio was the highest in III and IV groups and it was 0.9 in control group vs. 1.0 in I, 1.1 in II, 1.2 in III and 1.3 in IV group. Significant increase in gamma-glutamyl transpeptidase activity was observed in group III and IV, but alkaline phosphatase only in IV. Total protein concentration was significantly lower in group III and IV while albumin was significantly reduced in all four tested groups. In our patients there was a gradual increase of mean prothrombin time and APTT in groups II, III and IV compared to the control group (Table II).

Discussion

Chronic alcohol abuse causes structural and functional changes in the liver and leads to alcoholic liver disease (ALD). Alcoholic liver disease includes alcoholic fatty liver, alcoholic hepatitis (AH) and alcoholic cirrhosis. About 90% of alcohol dependent persons develop alcoholic fatty liver, 25% hepatitis, in approximately 15% liver cirrhosis and 10% liver cancer [4, 5]. Alcoholic liver disease, including alcoholic cirrhosis of the liver is a major risk factor for mortality in men aged 15-59 years and the eighth risk factor for mortality for all ages. The development of alcohol dependence is affected by the dose of alcohol consumed that for men is 60-80 g/day of pure alcohol and 20-40 g/day for women.

In order to identify alcohol dependent people and the detection of liver dysfunction, the liver enzymes activity and the composition of plasma proteins must be marked. AST and ALT aminotransferases are present in hepatocytes and are markers of liver cell damage because they are released into the bloodstream when hepatocytes are destroyed.

Researchers from the whole world have proved repeatedly that the ALT, AST and GGT are significantly higher in heavy drinkers than mild and

moderate drinkers [6-9]. GGT activity is significantly associated with alcoholic liver disease [10, 11]. It was also observed that the activity of ALP and GGT after abstinence period is reduced, but is still higher than those in the control group, indicating that they may be markers of chronic alcohol dependence [12]. Moreover, the increase in ALP activity is observed after many years of alcohol abuse [6, 13, 14].

In people with chronic alcohol disease, especially lasting longer than 20 years, the activity of aminotransferases is decreased due to loss of active liver tissue. In these patients, predominance of AST is observed due to deficiency of pyridoxal-5'-phosphate a necessary coenzyme for both aminotransferases. Its deficiency has a greater impact on the reduction of ALT than AST activity [7].

It is considered that the value of the De Ritis ratio > 1.5-2 is a diagnostic marker of alcoholic liver disease [10, 15, 16]. Kumar *et al*. studied the activity of liver enzymes in patients with non-alcoholic liver disease and in heavy and moderate drinkers with alcoholic liver disease. It was found that the activity of ALT, AST and ALP were highest in patients with non-alcoholic liver disease, and GGT activity and the De Ritis ratio were highest among heavy drinkers with alcoholic liver disease. In all tested groups, these parameters were significantly higher than in healthy controls. Analysis of all this parameters is very important in differentiation alcoholic from non-alcoholic aetiology of liver damage [7]. Total bilirubin was higher in the group of non-alcoholic liver damage, and the concentration of total protein and albumin levels was significantly lower in heavy drinkers compared to other groups.

Our study showed a gradual increase of alanine and aspartate transaminases activity with duration of alcohol dependence, with significantly higher values in patients dependent to alcohol for 6-20 years compared to persons from the control group. De Ritis ratio was significantly higher in all tested groups compared to control group, but mean value > 1 was observed only in group of patients who were alcohol dependent from 16 to 20 years. However, in Group IV, a six-fold increase in AST was observed, while the increase in ALT was only three-fold. On the other hand, a significant increase in GGT activity was observed in groups of patients dependent from 11 to 20 years compared to other tested and control groups. The relationship between the duration of alcohol dependence and alkaline phosphatase activity took on a U-shaped function, with a significantly higher values compared to the control group after 16 years of alcohol dependence. Moreover, we observed an almost linear positive correlation between the mean total bilirubin concentration and duration of alcoholism. Total protein concentration was significantly lower in patients dependent to alcohol from 11 to 20 years compared to other groups, while albumin has been significantly reduced in all groups compared to the control group, with the lowest value in patients with alcohol-dependence lasting from 16 to 20 years.

Albumin constitutes approx. 60% of all proteins in the human body. It is produced in the liver, which means that it reflects its function. Another important factor causing low serum albumin concentration in severely alcohol-dependent patients is malnutrition and destruction of the body [17]. Kok *et al*. showed decreased concentration of albumin in alcohol-dependent patients also, but they did not measure this parameter in the context of duration of dependence [18]. In contrast to our study, Alatalo *et al*. observed increase serum albumin concentration in the advanced alcohol dependants group compared to the control group. This phenomenon may be caused by increased synthesis of albumin before developing of hepatocyte dysfunction [9].

Important parameters reflecting liver function are changes in the coagulation system. In the present study, changes both in the extrinsic (PT) and intrinsic (APTT) coagulation pathway were observed. Our study has shown a gradual increase of the mean prothrombin time in group of alcohol abusers from six years, with essentially the longest mean PT in patients who were dependent from 16 to 20 years. The same results were obtained for the APTT. The extrinsic coagulation system is one of the parameters evaluated in the MELD score (Mayo End-Stage Liver Disease) indicating a risk of death within 30 days in patients with alcoholic cirrhosis [19].

Das *et al*., in their study comparing haematological parameters in patients with alcoholic and non-alcoholic fatty liver disease have shown the haematotoxic effect of chronic alcohol dependence, and significantly elevated mean prothrombin time in alcoholic patients [20].

The other good biochemical parameters of chronic alcohol abuse are carbohydrate deficient transferrin (CDT) as well as mean cor-

puscular volume (MCV). One of the causes of macrocytosis (increased MCV) may be chronic alcohol abuse. Based on this parameter, it is possible to deduce an intense consumption of alcohol even after a few months of abstinence. In spite of the very high specificity of the marker, the limitation is a number of other reasons that may cause an increase in MCV, e.g. cigarette smoking, folic acid and vitamin B_{12} deficiency [21].

Regardless of the primary cause, chronic liver disease results in its fibrosis and the excess deposition of matrix. There are both invasive and non-invasive methods for early detection of liver cirrhosis. An example of a modern non-invasive method is liver stiffness, which can be a rapid screening test for liver cirrhosis [22, 23]. Mueller *et al*. based on cohort of patients with chronic viral hepatitis C and alcoholic liver disease, found that liver stiffness (LS) cut-off values for histologically proved significant fibrosis/cirrhosis are influenced by abnormal transaminases with the strongest correlation with AST activity. These cut-off values increased as a function of median AST level [24]. Unfortunately, no liver stiffness measurements were performed to non-invasively and accurately assess fibrosis stage in all patients in this study.

Limitation of the study

In the present study, no MCV or transferase desial values were performed, making comparison with other parameters impossible. Liver structure was not assessed in the ultrasound image, nor liver stiffness examined, which is a significant limitation of the study and could allow to determine the percentage of patients with liver cirrhosis. The combination of many diagnostic methods significantly increases the sensitivity and specificity in detecting liver function disorders in the context of chronic alcohol abuse.

■ Conclusions

The adverse effect of chronic alcohol abuse on liver function is seen even after 1-5 years of alcohol dependence. After this time, the damage of hepatocytes is almost evident. After 16 years of alcohol dependence, liver function is seriously impaired, as is shown in a greatly reduced concentration of total protein and albumin. Negative alcohol effect on the liver is also seen in impaired clotting.

Conflict of interest/Konflikt interesów

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Ethics/Etyka

The work described in this article has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) on medical research involving human subjects, EU Directive (210/63/EU) on protection of animals used for scientific purposes, Uniform Requirements for manuscripts submitted to biomedical journals and the ethical principles defined in the Farmington Consensus of 1997.

Treści przedstawione w pracy są zgodne z zasadami Deklaracji Helsińskiej odnoszącymi się do badań z udziałem ludzi, dyrektywami UE dotyczącymi ochrony zwierząt używanych do celów naukowych, ujednoliconymi wymaganiami dla czasopism biomedycznych oraz z zasadami etycznymi określonymi w Porozumieniu z Farmington w 1997 roku.

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