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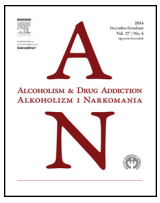

Original article/Artykuł oryginalny

Changes in concentration of visfatin during four weeks of inpatient treatment of alcohol dependent males

Zmiany stężenia wisfatyny u mężczyzn uzależnionych od alkoholu w czasie czterotygodniowego leczenia szpitalnego

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ABSTRACT

Introduction: Visfatin is a protein which belongs to the adiponectines, and exhibits insulinomimetic properties. A high concentration of visfatin may be directly related to an ongoing inflammatory process in the body. The aim of this study was to assess changes in the concentration of visfatin in relation to the intensity of alcohol craving and selected clinical characteristics in patients with alcohol dependency.

Materials and methods: The thirty-seven males enrolled in the study had been hospitalised due to alcohol dependence in the addiction treatment unit. In the first week and after four weeks of treatment, clotted blood samples were obtained to determine the concentration of visfatin and other biochemical parameters. Next, patients were divided into two groups – group 1 with a decrease and group 2 with an increase in the concentration of visfatin during the four weeks of treatment. The study used a socio-demographic and clinical scale, the Short Alcohol Dependence Data questionnaire (SADD) and an analogue alcohol craving scale. Additionally, the study considered measurements of waist-to-hip circumference ratio (WHR) and biochemical blood parameters.

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Results: There was a statistically significant difference between group 1 and group 2 in the concentration of visfatin (35.5 ng/ml *vs* 146 ng/ml) after four weeks of inpatient alcohol dependence treatment.
Discussion: Perhaps different pathophysiological processes were taking place (including inflammatory response) in patients with high and low visfatin concentration in the initial stage of the trial.
Conclusions: The dynamic of change in the concentration of visfatin during four weeks of abstinence is not associated with a reduction in craving for alcohol at the time and is associated with alcohol drinking and liver functioning.

S T R E S Z C Z E N I E

Słowa kluczowe:
wisfatyna
uzależnienie od alkoholu
głód alkoholowy

Wstęp: Wisfatyna jest białkiem (adipokiną), które wykazuje właściwości insulinomimetyczne. Wysokie stężenie wisfatyny może być związane z toczącym się w organizmie procesem zapalnym. Celem badań była ocena zmian stężenia wisfatyny w odniesieniu do doświadczania głodu alkoholowego i wybranych zmiennych klinicznych u osób uzależnionych od alkoholu.
Materiał i metody: W badaniu uczestniczyło 37 mężczyzn hospitalizowanych z powodu uzależnienia od alkoholu. W pierwszym oraz czwartym tygodniu leczenia pobrano krew do oznaczeń stężenia wisfatyny i innych parametrów biochemicznych. Badane osoby zostały podzielone na dwie grupy – grupa 1 ze spadkiem i grupa 2 ze wzrostem stężenia wisfatyny podczas czterech tygodni hospitalizacji. U badanych oceniono zmienne socjodemograficzne, kliniczne, głębokość uzależnienia od alkoholu (SADD), nasilenie głodu alkoholowego (skala analogowa 0-10) oraz WHR (*waist-to-hip circumference ratio*) i parametry biochemiczne krwi.
Wyniki: Wykazano znamienną statystycznie różnicę w stężeniu wisfatyny między grupą 1 a grupą 2 (35,5 ng/ml *vs* 146 ng/ml) po 4 tygodniach leczenia odwykowego.
Dyskusja: Prawdopodobnie u pacjentów z wysokim i niskim stężeniem wisfatyny w początkowym etapie leczenia (abstynencji) zachodziły odmienne procesy patofizjologiczne (w tym mniej lub bardziej zaznaczona odpowiedź zapalna).
Wnioski: Dynamika zmian stężenia wisfatyny podczas co najmniej czterech tygodni abstynencji nie jest związana z redukcją głodu alkoholowego w czasie, lecz ze spożywaniem alkoholu i funkcją wątroby.

Introduction

Visfatin is an adiponectin and plays an important role in the regulation of inflammatory, metabolic and immunological processes [1]. The role of visfatin in the pathogenesis of obesity, insulin resistance, metabolic syndrome, dyslipidemia, and related cardiovascular complications has attracted considerable scientific interest in recent years [2]. Adiponectines are also involved in the pathogenesis of chronic liver disease caused by non-alcoholic fatty liver disease and the viral hepatitis. They sustain the inflammatory processes and enhance periportal fibrosis [3].

Similar pathological processes occur in alcohol abusers, who commonly exhibit an abnormal metabolism of carbohydrates and lipids including insulin resistance and hyperlipidaemia [4, 5]. Visfatin concentration, and also leptin concentration, is higher in obese and diabetic individuals. It is related to the body fat tissue content [6, 7]. These observations are confirmed by FINRISK study which showed that alcohol consumption increases the risk of obesity [8]. Measurement of the changes in

concentration of visfatin could be an important biochemical marker of the metabolic processes occurring in alcohol dependent persons (both during acute excessive alcohol intake and during the treatment of alcohol dependency, abstinence, and recovery) [9]. Studies indicate that appetite-regulating peptides have influence on the feeling of alcohol craving [10]. For instance, studies have shown an association between insulin concentrations and the results of the severity of craving among actively drinking individuals, what means that insulin may be involved in the processes of neurobiological craving for alcohol and addiction [9]. Thus, it can be expected that the concentration of visfatin as a protein that compensates adjustment of insulin carbohydrate [11] may directly or indirectly result in the perception of craving.

Visfatin is adiponectin the features of which we are only just beginning to understand. However, the knowledge about this protein and metabolic processes in which it participates acquired so far suggests that it may become a notable marker of health problems and the risk of relapse among alcohol dependent persons. The pathophysiological role of visfatin may be related to its insulin-like mechanism of action. This may stimulate the activity of the hunger centre which in turn enhances alcohol craving and also promotes obesity.

The aim of this study was to assess changes in the concentration of visfatin in relation to the intensity of alcohol craving and selected clinical and anthropometric characteristics in alcohol dependent patients. The assessments were performed at the start of the inpatient alcohol treatment and then again after four weeks.

Materials and methods

The thirty-seven male patients hospitalised in the addiction treatment unit due to alcohol dependence (ICD-10) were enrolled in the study. The twenty-eight males (mean age 31) from the general population were examined as a control group. Subjects suffering from alcohol withdrawal syndrome or metabolic disorders such as diabetes were excluded from the study.

The concentration of visfatin was measured in all patients in the first and fourth week of hospitalisation as it was in the control group. During four weeks of treatment, an increase of the concentration of visfatin was observed in some patients, and a decrease in others. The question arises: Can changes in the experience alcohol craving and clinical variables be attributed to changes in visfatin concentration in the time of abstinence?

The studied subjects were divided into two groups depending on whether there was a decrease of the visfatin concentration – group 1 of 21 inpatients (57% of the study population, mean age 41) or an increase – group 2 of 16 inpatients (43% and 38 respectively).

The patients were examined twice – once in the first and once in the fourth week of hospitalisation. The period of four weeks (between the first and second examination) was chosen arbitrarily to assess changes of the variables tested during therapy. All permanent rehabilitation took no more than 8 weeks, so tests would be repeated after 5–6 weeks, but in this period of treatment the risk of premature therapy finishing and stress before the end of hospitalisation may increase.

Socio-demographic data (age, marital status, employment) and information regarding severity of alcohol craving and alcohol consumption during 30 days before the assessment were obtained from all the subjects (some patients could participate in detoxification therapy but it was not considered in this study, also the time of subjects abstinence was not taken into account). Alcohol craving was assessed using an analogue scale (visual analogue scale) where 0 is “no alcohol craving” and 10 “extreme alcohol craving”. This scale was selected due to its simplicity, understanding (does not require complicated cultural adaptation) and easiness in evaluation of intensity of alcohol craving changes at the time. The severity of alcohol dependence was assessed using SADD (Short Alcohol Dependence Data questionnaire) [12]. Higher scores indicate higher intensity of dependence. The waist-to-hip circumference ratio (WHR) was also measured. Values of >0.9 may indicate abdominal obesity [13].

In the first week of treatment and after four weeks, a clotted blood samples were obtained to determine the concentration of visfatin (test EIA – Enzyme-linked Immunosorbent Assay, USCN Life Science Inc.). The blood samples were centrifuged at 4°C and 3600 rev/min. The serum obtained was stored at −80°C. In the first week of hospitalisation, the activity of alanine aminotransferase (ALT), gamma-glutamyl transferase (GGTP), and concentration of glucose, triglycerides, total cholesterol were evaluated.

Mann-Whitney *U* test, Fisher's exact test, and the Wilcoxon test using SPSS 20 software were used for

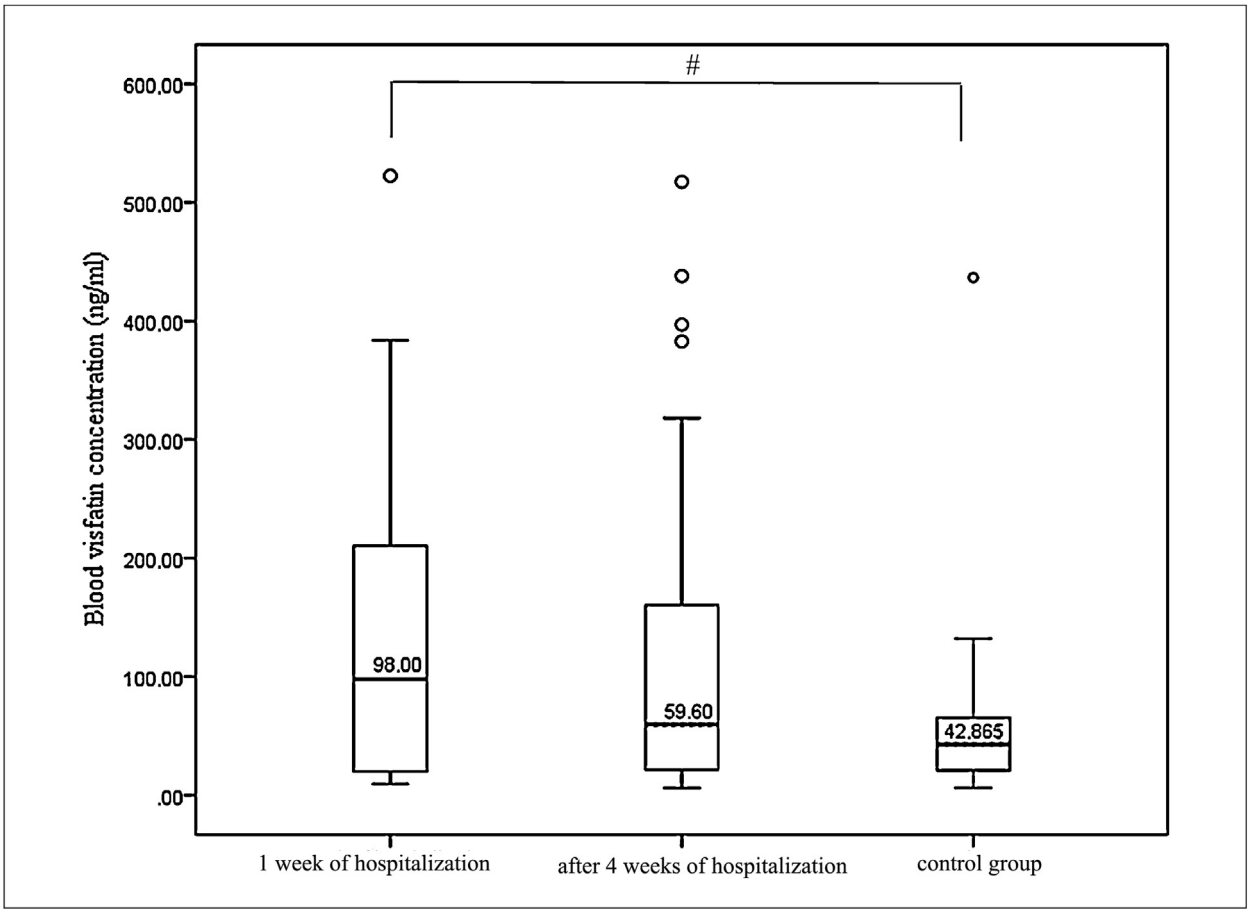

Fig. 1. Comparison of visfatin concentration between the groups of inpatient alcohol dependence treatment in the first week of hospitalisation ($n = 37$), after four weeks of hospitalisation ($n = 37$) and control group ($n = 28$)
Mann-Whitney U test, where # $p \leq 0.05$

statistical analysis of the results. Variables were described by median and interquartile range (quartile) due to the small number of respondents and the asymmetry of variables distribution. The level of statistical significance was considered at $p \leq 0.05$.

The study was approved by the Ethics Committee and funded by a university grant.

Results

The visfatin concentration in the first week and after four weeks of hospitalisation

In the first step, we analysed the differences of *visfatin* concentration between the group of alcohol dependent inpatients in the first week and after four weeks of hospitalisation and persons of the control group (Fig. 1).

Fig. 1 showed that the highest concentration of visfatin was in patients in the first week (98.0 ng/ml), a lower level in patients in the fourth week (near 60 ng/ml) and the lowest in the control group (near 43 ng/ml). We observed a statistically significant difference in the concentration of visfatin between two trials, specifically in subjects in the first week and those from the control group ($p < 0.05$).

Observation of a decrease (group 1) or an increase (group 2) of visfatin concentration during the four-week hospitalisation

In the evaluation of obtained results, it turned out that in the part of subjects where the concentration of visfatin was changed, in some it was higher and in others lower (between the first and second trial). This was the reason for the division of the studied population into group 1 and group 2.

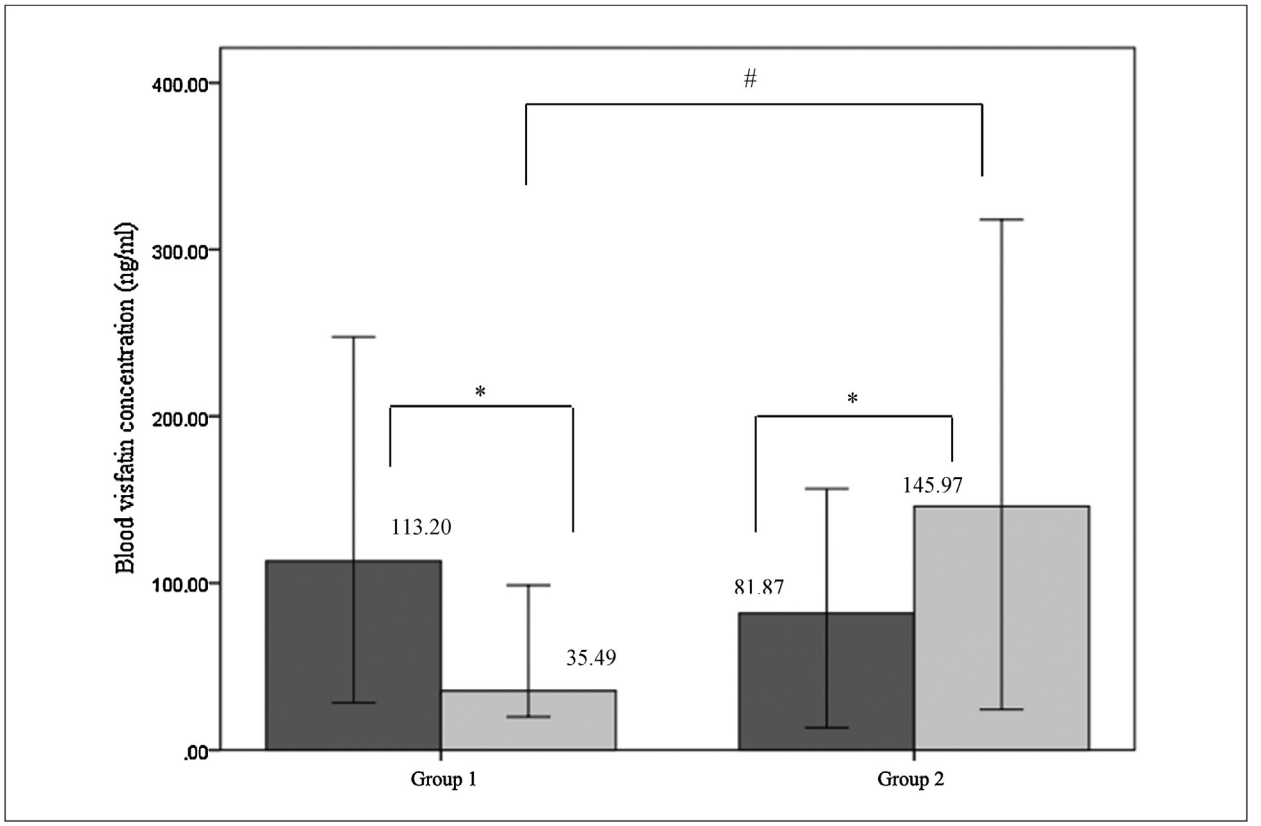

Fig. 2. Comparison of visfatin concentration between the two groups of subjects – with a decreased (group 1) and with an increased visfatin concentration (group 2) during the four-week inpatient alcohol dependence treatment
Dark colour means the first week of hospitalisation, bright – re-examination after four weeks of hospitalisation
Wilcoxon test, where * $p \leq 0.001$; Mann-Whitney U test, where # $p \leq 0.05$

We observed (Fig. 2) that the individuals from both groups (1 and 2) had similar visfatin concentration at the beginning of treatment ($p = 0.141$). The change in the visfatin concentration was a statistically significant in both groups after the four-week treatment and there was a statistically significant difference in visfatin concentration between both groups in the fourth week of hospitalisation (35.5 ng/ml *vs* 146 ng/ml).

The demographic data of two groups of patients

The demographic data of group 1 and 2 are shown in Table I. Data indicate that subjects from group 2 with an increased visfatin concentration compared to the control group were more frequently unemployed (78.6% and 37.5% respectively) and more frequently single (55.6% and 25% respectively).

The clinical characteristics of two groups of patients

The clinical data of group 1 and 2 are shown in Table II. It illustrates age and clinical characteristics (severity of dependence, intensity of alcohol craving, laboratory indices, and WHR) of each of the two patient groups.

We observed (Table II) that between the subjects from group 1 with a decreased visfatin concentration and those from group 2 with an increased visfatin concentration there was no a statistically significant differences concerning characteristics such as average age (41 *vs* 38.8), duration of alcohol dependence (10 years *vs* 10 years), SADD scores (21 *vs* 24), triglycerides concentration (131 mg/dL *vs* 118.5 mg/dL), total cholesterol concentration (226 mg/dL *vs* 229 mg/dL), and WHR at the beginning (1.0 *vs* 1.0) and after four weeks of treatment (0.94 *vs* 0.97). In the individuals from both groups the intensity of alcohol

Table I
Socio-demographic characteristics of each of the three patient groups (decreased visfatin concentration, increased visfatin concentration and control) during the four-week inpatient alcohol dependence treatment

Socio-demographic characteristics	Group 1 ($n = 21$)	Group 2 ($n = 16$)	Control group ($n = 27$–28)
Place of residence			
Rural	4 (19.0%)	2 (12.5%)	3 (10.7%)
Urban	17 (81.0%)	14 (87.5%)	25 (89.3%)
Marital status			
Married	12 (57.1%)	4 (25.0%)	15 (55.6%)
Single	9 (42.9%)	12 (75.0%)	12 (44.4%)
Source of income			
Unemployed	6 (28.6%)	6 (37.5%)	5 (17.8%)
Employed	13 (61.9%)	6 (37.5%)	22 (78.6%)**
Pension	2 (9.5%)	4 (25.0%)	1 (3.6%)*

Group 1 – subjects with decreased concentration of visfatin during the four-week alcohol dependence treatment.
Group 2 – subjects with increased concentration of visfatin during the four-week alcohol dependence treatment.
Fisher's exact test, a statistically significant difference between: group 2 *vs* control group, where * $p \leq 0.05$ and ** $p \leq 0.01$.

Table II
Clinical characteristics of the groups of subjects with a decreased concentration of visfatin (group 1) and an increased concentration of visfatin (group 2) during the four-week inpatient alcohol dependence treatment

Clinical characteristics	Group 1 ($n = 21$)			Group 2 ($n = 16$)		
		Quartiles			Quartiles	
	M	I	III	M	I	III
Age (years)	**41.00**	35.63	50.50	**38.79**	32.50	51.25
Duration of dependence (years)	**10.00**	5.50	16.50	**10.00**	6.25	12.00
Intensity of alcohol craving (scale 0–10) I	**7.00****	5.00	8.00	**6.50****	3.50	9.75
Intensity of alcohol craving (scale 0–10) II	**0.00**	0.00	4.50	**0.00**	0.00	8.00
SADD (scores) I	**21.00**	17.75	26.50	**24.00**	20.00	27.00
Consumption of alcohol during 30 days prior to hospitalisation (number %)						
Yes		19 (90.5%)			8 (50%)##	
No		2 (9.5%)			8 (50%)	
ALT (U/L) I	**40.00**	25.50	58.50	**25.00**	18.50	36.25
GGTP (U/L) I	**79.00#**	44.50	136.50	**40.00#**	27.00	68.00
Serum glucose (mg%) I	**87.00**	82.50	93.50	**89.00**	85.00	95.50
Triglycerides (mg/dL) I	**131.00**	100.50	178.50	**118.50**	96.75	198.00
Total cholesterol (mg/dL) I	**226.00**	197.50	278.50	**229.00**	197.25	252.50
WHR I	**1.00***	0.91	1.00	**1.00****	0.90	1.00
WHR II	**0.94***	0.90	1.00	**0.97****	0.90	0.99

I – assessment at the first week of hospitalisation, II – re-assessment at the fourth week of hospitalisation.
Wilcoxon test, where * $p = 0.099$, ** $p \leq 0.05$; Mann-Whitney U test or Fisher's exact test, where $^{\#}$ $p \leq 0.05$, $^{\#\#}$ $p \leq 0.01$.

craving (scale 0 to 10) was comparable at the beginning (7.0 *vs* 6.5) and at the end (0.0 *vs* 0.0) of treatment.

There was a statistically significant reduction in the alcohol craving intensity in both groups after the treatment ($p \leq 0.05$). The average alanine aminotransferase (ALT) concentration was higher in group 1 (40 μ/L *vs* 25 μ/L). Similarly, the gamma-glutamyl transferase (GGTP) concentration was higher in group 1 (79 mg/dL *vs* 40 mg/dL). A statistically significant reduction of WHR during the treatment was observed in both groups (1.0 *vs* 0.94 and 1.0 *vs* 0.97, respectively). Ninety percent of patients with a reduced visfatin concentration during the treatment (group 1), and 50%

of patients with an increased visfatin concentration (group 2) consumed alcohol during 30 days before hospitalisation.

Discussion

The study showed that subjects had higher visfatin concentration in the first week of treatment than after four weeks, and also higher than in the control group. But the analysis of outcomes showed that in some subjects a decrease and in the others an increase in visfatin concentration followed during the four-week hospitalisation (four-week abstinence). It was very interesting which changes in the clinical characteristics were connected with the decreasing (group 1) or increasing trend (group 2) of visfatin concentration during the treatment. In both groups there was a statistically significant change of visfatin concentration during the treatment, and between group 1 and group 2 there was a statistically significant difference of visfatin concentration only in the fourth week of treatment. The concentration of visfatin, when studied subjects at the beginning of treatment were compared with the control group was lower in males from the control group. These males consumed less alcohol, were younger and characterised by a lower WHR. The concentration of visfatin was also lower in the subjects after four weeks of abstinence.

Jurdana et al. found that significant predictors of visfatin concentration were low physical activity among men and also an activity of C-reactive protein. The latter is independent of gender [6].

An association between visfatin and C-reactive protein levels may explain the phenomenon of different trends of visfatin concentration in alcohol dependent subjects during their four-week inpatient treatment. Perhaps different pathophysiological processes were taking place (including inflammatory response) in the patients with high (decreasing trend during the treatment) and low (increasing trend) visfatin concentration in the initial stage of the trial. Heng-cai et al. in research on rats showed that visfatin concentration was higher by strong exposure to ethanol and visfatin concentration was correlated positively with visceral adipocyte tissues [14]. According to Ozkaya et al. the concentration of visfatin in plasma is associated with body mass, metabolic syndrome or diabetes [15], but according to different study there is no correlation between visfatin concentration and metabolic or anthropometric variables [16].

The studied subjects (from group 1 and 2) showed similar changes in the clinical characteristics during the four-week inpatient treatment. There was decrease in WHR (waist-to-hip circumference ratio) and intensity of alcohol craving. None of the groups of patients showed any statistically significant differences in WHR or alcohol craving, either at the start of alcohol dependence treatment or after four weeks of the treatment. In the group of subjects with an increased concentration of visfatin, there was no increase in WHR. This differs from the results of other studies indicating a significant positive link between visfatin concentration and body fat percentage [17]. As researches showed, an increase of visfatin concentration is observed in metabolic syndrome (where anthropometric indices are higher) [18] and in diabetes type II [3].

The literature suggests that a high concentration of visfatin may be directly related to an ongoing inflammatory process in the body [3]. However, as other authors suggest, the concentration of circulating visfatin and liver visfatin mRNA level are reduced in patients with hepatitis [17]. Subsequent analysis showed that the subjects with low concentration of visfatin at the beginning of treatment differ from those with a higher concentration of visfatin [17]. They (the first ones) characterised with lower alcohol consumption and lower liver enzymes activity during 30 days before the trial. There is decreased concentration of visfatin in blood serum in patients with liver cirrhosis.

Heng-cai et al. showed that changes of visfatin, leptin and adiponectin can be independent of alcohol related liver injury [14]. Visfatin concentration seems not to be related to insulin resistance but rather to the reduced glucose metabolism (when compared to healthy people), for example in liver cirrhosis [17]. The concentration of visfatin is positively correlated with the blood ketone index and NADH ++H+ generation [17].

According to Wu and Cederbaum [19], the reduced form of nicotinamide adenine dinucleotide (NAD++H+) is generated in a cytoplasm of hepatocytes during a transformation of ethyl alcohol into acetate. This may result in the suppression of "mitochondrial oxidation", over-production of triglycerides and lactate in the liver, and also lead to an excess of free fatty acids [19, 20]. It is likely that visfatin stimulates insulin, interleukin-6 (IL-6), tumour necrosis factor α (TNFα) secretion, and also induces the synthesis of nicotinamide adenine

dinucleotide [3]. It was observed that alcohol dependent subjects had higher insulin and glucose levels in response to beer consumption than those not dependent [21].

Zilkens et al. confirmed that there is a proportional increase in insulin concentration in blood serum and homeostatic model assessment (HOMA) index values to the amount of consumed alcohol [22].

A statistically significant positive correlation between concentration of insulin and intensity of alcohol craving (in subjects actively consuming alcohol) has also been demonstrated in other studies. This indicates that insulin may be involved in neurobiological processes of alcohol craving and alcohol dependence [9, 23].

Based on the analysis of data obtained in this study, it can be assumed there is an association between the serum concentration of visfatin and alcohol craving. This problem requires further research because of the importance of alcohol craving in promoting relapse of alcohol drinking behaviour.

Clinical benefits: Evaluation of concentration of visfatin in alcohol dependent patients attending an addiction treatment unit may be an important predictor of biochemical changes occurring due to changes in anatomical and secretory adipocytes. Thus, the assessment of changes in the concentration of visfatin will help evaluate the risk of obesity, insulin resistance, occurrence of inflammatory processes and fatty liver disease [24, 25] in order to reduce health damage. However, according to research the above-mentioned assessment did not detect patient exposure to alcohol craving effectively.

Limitations of research: Small group of respondents, lack of assessment of selected biochemical marks in the second stage of the study, no application of an additional questionnaire to measure the severity of alcohol craving and verification of patients in terms of psychotropic medications, and in terms of other factors such as stress and social relations that could have an impact on the willingness for alcohol consumption.

Conclusions

It was found that almost 57% of studied subjects had a decrease and 43% an increase in the concentration of visfatin after the four-week alcohol dependence inpatient treatment.

There was a significant reduction in the intensity of alcohol craving during the four-week alcohol dependence inpatient treatment in both groups – with a decreased and an increased visfatin concentration.

Subjects with a decreased concentration of visfatin consumed alcohol more often during 30 days prior to hospitalisation and had higher activity of GGTP when compared to subjects with an increased concentration of visfatin after the four-week alcohol dependence inpatient treatment. Higher GGTP activity suggests more advanced hepatitis.

Authors' contributions/Wkład autorów

Study design: D. Czarnecki, Z. Rosińska, E. Żekanowska, M. Ziółkowski, E.J. Gorzelańczyk, A. Długosz, J. Budzyński. *Data collection*: D. Czarnecki, Z. Rosińska, B. Góralczyk, A. Długosz. *Statistical analysis*: D. Czarnecki, E. Żekanowska, M. Ziółkowski, B. Góralczyk. *Data interpretation*: D. Czarnecki, E.J. Gorzelańczyk, M. Kunc, B. Łangowska-Grodzka, K. Opozda. *Acceptance of final manuscript version*: E. Żekanowska, M. Ziółkowski, E.J. Gorzelańczyk, B. Łangowska-Grodzka, K. Opozda. *Literature search*: D. Czarnecki, Z. Rosińska, A. Długosz. *Funds collection*: D. Czarnecki, M. Ziółkowski.

No ghostwriting and guest authorship declared.

Conflict of interest/Konflikt interesów

None declared.

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Ethics/Etyka

The Biomedical Commission of the Collegium Medicum Nicolaus Copernicus University in Toruń approved this research (no KB 243/2008).

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 use of scientific purposes; Uniform Requirements for manuscripts submitted to biomedical journals; the

ethical principles defined in the Farmington Consensus of 1997.

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