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IGF-I and IGFBP-3 before and after inpatient alcohol detoxification in alcohol-dependent subjects

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A Study Design
B Data Collection
C Statistical Analysis
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Summary

Background: It is unclear whether alcohol detoxification has an effect on factors that are involved in growth, metabolic functions and cell proliferation. Alcohol abuse is associated with low IGF-I levels that tend to rise after alcohol withdrawal. There is a paucity of studies on the course of IGFBP-3 (the main binding protein for IGF-I) after alcohol detoxification.

Material/Methods: We prospectively assessed IGF-I and IGFBP-3 changes at the time of admission and after 4 to 6 weeks of detoxification in an inpatient alcohol detoxification facility in 118 alcohol-dependent subjects given a regular hospital diet. No participants dropped out of the study.

Results: Changes in IGF-I after alcohol detoxification showed a marked dimorphism in altered hepatic biochemistry upon admission, with a rise in those with normal liver enzymes upon admission (p=0.016, Kruskall-Wallis) and a drop in those with elevated liver enzymes upon admission (p=0.05); the latter was noted in subjects that had consumed alcohol close to the time of admission. Overall, however, IGF-I and IGFBP-3 were within normal limits for most subjects both upon admission and after alcohol detoxification; no significant differences were detected among the examined parameters in men *vs.* women, and there were no significant correlations of IGF-I, IGFBP-3 or the IGF-I/IGFBP-3 molar ratio with BMI or age.

Conclusions: Regardless of hepatic enzymes' elevation, alcohol detoxification had overall slight effects on IGF-I and IGFBP-3.

key words: **alcohol • insulin-like growth factor type-1 (IGF-1) • IGF-binding proteins**

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Background

The nefarious effects of alcohol on health are numerous; the mechanisms involved are varied and are the subject of intense study. Dysregulation of the liver-produced insulin-like growth factor-I axis (IGF-I) has been associated with growth or metabolic disturbances and even cancer development [1–7]; IGFBP-3 (the major binding protein of IGF-I, which is mainly produced by the liver, although it is also produced by most other tissues [8]) inhibits IGF-I's actions [9]. In general, alcohol abuse is associated with low IGF-I levels that tend to rise after alcohol withdrawal [10,11]. Although many studies have focused on alcohol-induced endocrine/metabolic changes, the impact of alcohol abuse on IGF-I along with IGFBP-3 has rarely been assessed [10,12–14]. Acute alcohol abuse has not been shown to have an effect on IGFBP-3 [15], whereas chronic moderate alcohol use has been shown to be associated with a moderate increase in IGFBP-3 [16]. Consequently, it would be interesting to evaluate whether alcohol withdrawal has any effect on factors that are involved in metabolic disturbances and cell proliferation in humans, but to the best of our knowledge the effect of alcohol detoxification on IGFBP-3 in alcohol-dependent subjects has not yet been presented. We can hypothesize that alcohol detoxification in alcohol-dependent subjects may lead to a decrease in the IGF-I/IGFBP-3 ratio. Thus, the aim of the present study was to assess IGF-I and IGFBP-3 changes at the time of admission and after 4 to 6 weeks of detoxification in an inpatient alcohol treatment facility.

Material and Methods

The sample of the study consisted of 118 alcohol-dependent individuals (84 men, 34 women; mean age ±SD: 46±11 years; mean BMI: 23.7±3.3 kg/m^2; duration of alcohol abuse mean ±SD =20.5±9.0 years, for men: 23.2±8.6 years and for women 13.8±6.0 years) who had consecutively contacted the Drug and Alcohol Addiction Clinic of the Athens University Psychiatric Clinic at the Eginition Hospital in Athens, Greece. All patients fulfilled the DSM-IV diagnostic criteria for alcohol abuse/dependence [17], and were admitted on a voluntary basis at this specialized department for dry inpatient alcohol detoxification. Detailed information on the objectives of the study and the research-therapeutic protocol was provided to all subjects and written informed consent was obtained from each participant. All procedures followed were in accordance with the ethical standards of the local committee on human experimentation of our institution ("Committee on Medical Ethics of the Eginition Hospital") and with the Helsinki Declaration of 1975, as revised in 1983 [18]. Participants had to fulfill the following criteria: a) age 20–75 years, b) absence of serious physical illness (and in particular cirrhosis), as assessed through medical history, physical examination, routine laboratory evaluation, as well as hepatic function tests and ultrasound imaging, c) absence of another pre- or co-existing major psychiatric disorder on the DSM-IV axis I, and d) absence of other substance abuse.

The inpatient alcohol detoxification protocol was started upon admission to the ward and was completed after a stay of 4–6 weeks in the ward. This is a highly structured inpatient detoxification program, which is closely attached to an outpatient alcohol detoxification service. People attend this program on a voluntary basis and must sign a therapeutic contract. Also, the close relationship with experienced therapists prevents stopping therapy. Therefore, a high retention rate is expected in this program and discontinuation is rare. In our population, no participants dropped out of the study. The subjects were given a regular hospital diet (about 1800–1900 Kcal/day, with 2 servings of vegetables and 3 servings of fruit per day). The protocol included vitamin replacement (vitamins C, E and B complex) and oral diazepam (30–60 mg in divided doses), with gradual taper-off over a week. Thereafter, participants were given brief cognitive-behavioral psychotherapy consisting both of individual sessions (twice a week) and family interventions (once every 2 weeks).

The Schedules for Clinical Assessment in Neuropsychiatry (SCAN) was used for diagnosis [19] and the Composite International Diagnostic Interview (CIDI) [20] was used for the assessment of pattern of alcohol abuse, potential major life problems related to alcohol consumption and the occurrence of withdrawal symptoms in the past. The time of the subjects' last drink was noted and information related to frequency and quantity of alcohol use in the past year was collected. All data pertaining to alcohol use were self-reported; to ascertain the accuracy of the information, a relative was also interviewed to corroborate the current status and psychiatric history. No formal analysis of the degree of corroboration was obtained; the overall opinion in the relevant literature is that the correspondence between these 2 sources is high [21,22].

Fasting blood from all patients was obtained within 24 h upon admission and after completion of detoxification (4–6 weeks). Upon admission, hepatic enzymes (aspartate aminotransferase; AST, alanine transaminase; ALT, gamma glutamyl transpeptidase; γGT) and mean corpuscular volume (MCV) as biological markers of alcohol abuse (albeit with low sensitivity) [23–25] and serum IGF-I and IGFBP-3 were measured. The latter 2 markers were measured with immunoradiometric assays (Immunotech-Beckman-Coulter, Praha, Czech Republic); for IGF-I the sensitivity was 2 ng/mL, the intra-assay coefficient of variation (CV) was <5.6% and the interassay CV was 9.0%; for IGFBP-3 the sensitivity was 5 μg/mL, the intra-assay CV was <3.9% and the interassay CV was 7.6%) [26,27]. The measurements for IGF-I and IGFBP-3 were run in duplicates. AST, ALT, γGT, IGF-I and IGFBP-3 were also measured after 4–6 weeks of observed abstinence. We also calculated the molar IGF-I/IGFBP-3 ratio (1 ng/mL IGF-I = 0.130 nmol IGF-I and 1 μg/mL IGFBP-3 =36 nmol IGFBP-3 [28]), a surrogate measure of free IGF-I [29] that reflects biologically active IGF-I [30]. Because the distributions of IGF-I and IGFBP-3 were skewed, we chose non-parametric, distribution-free methods for analysis. Statistical analyses were done with the Kruskall-Wallis and Spearman's tests.

Results

Baseline

Most subjects (75%) had some degree of hepatic enzyme elevation upon admission (at least 1 enzyme measurement above the upper normal limit).

Table 1. Levels of IGF and IGFBP-3 upon admission and after 4–6 weeks of alcohol detoxification according to hepatic biochemistry and timing of last alcohol ingestion; values are given as medians and 25–75th percentiles are given in parentheses.

		Elevated hepatic enzymes upon admission (n=88)		Normal hepatic enzymes upon admission (n=30)	
	Alcohol before admission	t=0	t=4–6 weeks	t=0	t=4–6 weeks
IGF-I (ng/mL)	≤6 hours	231 (144–741)*	155 (113–248)*	139 (116–186)	213 (155–273)
	≥6 hours	192 (128–786)$^{+}$	142 (102–547)	117 (106–132)**,$^{+}$	151 (116–160)**
IGFBP-3 (µg/mL)	≤6 hours	3.40 (1.62–4.40)$^{++}$	2.00 (1.35–4.25)	3.03 (2.06–4.40)$^{\#}$	4.05 (2.51–4.65)
	≥6 hours	2.08 (1.30–2.71)	1.83 (1.13–2.20)	1.21 (0.65–2.19)$^{++,\#}$	1.14 (0.65–3.49)
IGF-I/IGFBP-3 molar ratio	≤6 hours	0.63 (0.14–1.53)	0.24 (0.16–0.91)	0.25 (0.14–0.60)	0.20 (0.16–0.35)
	≥6 hours	0.35 (0.13–1.17)	0.56 (0.31–0.98)	0.37 (0.23–0.63)	0.42 (0.24–0.67)

Normal limits: AST < 35 IU/L; ALT <35 IU/L; γGT <50 IU/L; * p=0.050; ** p=0.016; $^{+}$ p=0.044, $^{++}$ p=0.047, $^{\#}$ p=0.013; Kruskall-Wallis.

Table 2. Hepatic biochemistry of subjects (n=118) included in the study (values are presented as medians and 25–75th percentiles are given in parentheses), MCV and reported alcohol consumption during the last year (values are given as means ±SD).

	AST (IU/L)	ALT (IU/L)	γGT (IU/L)	MCV (fL)	Alcohol quantity (g/day)
Preceding admission to detoxification	–	–	–	–	208±112
Upon admission	38 (28–64)	35 (25–51)	73 (40–193)	95±6	–
After 4–6 weeks of detoxification	29 (23–38)	29 (20–38)	48 (32–59)	–	–

Normal limits: AST < 35 IU/L; ALT < 35 IU/L; γGT < 50 IU/L; MCV: 80-95 fL.

The self-reported time of the subjects' last drink was categorized into 2 groups: no alcohol for at least 6 hours before admission (n=74) and alcohol ingestion closer to admission (n=44); the 6-hour limit was chosen taking into account the half-life of ethanol – approximately 3-6 hours [31].

Subjects with elevated hepatic enzymes upon admission and who had consumed alcohol more than 6 hours before entering the hospital had higher IGF-I compared to those that had not consumed alcohol recently and had normal liver enzymes (Table 1). Subjects that had consumed alcohol in the 6 hours preceding admission had higher IGFBP-3 levels compared to those that had not consumed alcohol in the same time period (this difference was more important when comparing subjects with elevated hepatic enzymes with subjects with normal hepatic enzymes on admission). No significant difference was noted in the IGF/IGFBP-3 molar ratio (Table 1).

After alcohol detoxification

At the end of the detoxification period the hepatic enzyme elevation persisted (albeit slightly) in fewer than half of the subjects (47%) (Table 2). The drop in AST, ALT and γGT after 4-6 weeks of detoxification corroborates abstinence from alcohol [32].

In subjects with normal liver enzymes upon admission and no alcohol consumption for more than 6 hours, a significant rise in IGF-I was noted after 4–6 weeks of abstinence; a significant drop in IGF-I was noted at the same time for subjects with elevated liver enzymes and alcohol consumption within the 6 hours preceding admission (Table 1). Changes were noted for IGFBP-3 and the IGF-I/IGFBP-3 molar ratio, but this did not reach statistical significance (Table 1).

Overall IGF-I and IGFBP-3 were within normal limits for most subjects both upon admission and after alcohol detoxification; no significant differences were detected among the examined parameters in men *vs.* women; there were no significant differences in BMI in subjects with normal hepatic biochemistry *vs.* those with impaired hepatic biochemistry, and no significant correlations of IGF-I, IGFBP-3 or the IGF-I/IGFBP-3 molar ratio with BMI or age were found (data not shown). Furthermore, Spearman's correlations that were run for IGFBP-3 *vs.* IGF-I levels using hepatic enzymes' levels, timing of last drink before admission and timing of sampling as dummy variables did not reach statistical significance (Figure 1).

Discussion

In this study changes in IGF-I after alcohol detoxification showed a marked dimorphism in relation to hepatic enzymes'

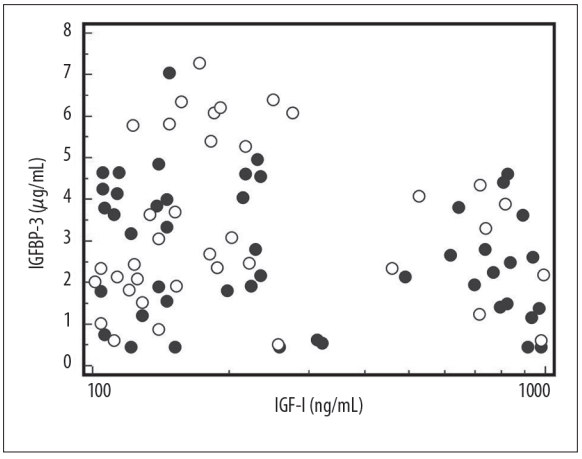

Figure 1. IGFBP-3 levels *vs.* IGF-I levels in subjects with elevated hepatic enzymes upon admission (closed circles) and subjects with normal hepatic enzymes upon admission (open circles).

status, with a rise in those with normal liver enzymes upon admission and a drop in those with elevated liver enzymes upon admission. Nevertheless, the IGF/IGFBP-3 molar ratio did not change significantly, and the hypothesis that alcohol withdrawal in alcohol-dependent subjects would lead to a decrease in the IGF-I/IGFBP-3 ratio was not proven.

In unselected populations there is usually a negative correlation between hepatic enzymes and IGF-I and a positive correlation between hepatic enzymes and IGFBP-3 (independent of alcohol use) [33]. Binge drinking transiently decreases IGF-I in experimental models but has no appreciable effect on IGFBP-3 [34]. Alcohol-dependent individuals have been shown to have lower IGFs and IGFBP-3 levels compared to normal subjects [10], whereas in most epidemiological and experimental studies dietary alcohol intake has been negatively correlated with IGF-I levels [13,14], and positive or negative correlations have been found with IGFBP-3 levels [12–14,35]. In previous studies [11,36] similar changes in IGF-I after alcohol detoxification were noted, as in our study. The fact that some of our subjects had IGF-I levels that dropped after abstinence is congruous with the observed variations of IGF-I in relation to hepatic enzymes' levels.

In published studies, liver-produced IGF-binding protein (IGFBP-1) showed a drop after alcohol detoxification and increased the IGF/IGFBP-1 ratio. However, it is IGFBP-3 that mostly binds IGF-I (approximately 75% of it) and modulates and/or inhibits the actions of IGF-I [9]. To the best of our knowledge there have been no other studies on IGFBP-3 and alcohol detoxification. In our subjects, the observed variation in IGFBP-3, like that of IGF-I, seems related to levels of hepatic enzymes.

No significant correlations of IGF-I, IGFBP-3 or the IGF-I/IGFBP-3 molar ratio with BMI or age were found. This is not surprising, since such correlations have been mostly and consistently reported in children and adolescents [37–41].

The interplay of IGF-I and IGFBP-3 in health and in a multitude of pathologies (including neurodegenerative diseases, growth disorders and cancer) is the subject of intense research [4–7,9]; IGFBP-3 has antiproliferative and proapoptotic effects and may possibly protect from cancer [9]. Thus, changes of IGF-I and IGFBP-3 in alcohol-dependent subjects are of interest, because alcohol abuse has been consistently linked to neoplasia risk [42]. The existence of autoregulatory mechanisms that control the bioavailability of IGF-I bound to IGFBP-3 has been suggested [43]; they may be protective against neoplasia to some extent (cancer has been linked to down-regulation of IGFBP-3 production) [44].

This study has limitations that need to be pointed out. There were no cirrhotic subjects included. The subjects' weight at the time they were discharged from the hospital was not routinely recorded and was not included in the analyses (although for those subjects for whom it was available it did not show any appreciable difference from the weight upon admission, and the analyses of BMI *vs.* IGF-I, IGFBP3 levels did not produce significant results). Other limitations have to be noted, particularly with regard to the assays used. One explanation for the few high IGF-I levels in the group with elevated hepatic enzymes on admission may be interference by IGF-binding protein-1 in the IGF-I assay [26]. Furthermore, the observed divergence in the responses of IGF-I and IGFBP-3 in subjects with and without elevation of hepatic enzymes may be explained by the presence of IGFBP-3 fragments, which are also measured in the assay used [45]. Another caveat is that recent alcohol intake may induce proteolysis of IGFBP-3 and consequently raise IGF-I [46]. Finally, this study did not assess the status of other factors involved in IGF-I's physiology. One such factor in particular is the liver-produced acid-labile subunit (ALS) that binds circulating IGF-I with IGFBP-3 in 150 kDa ternary complexes, restricts it to the circulation, and prolongs the half-lives of IGF-I and IGFBP-3 [47]. Fasting, malnutrition or cirrhosis lower serum ALS [47]. To the best of our knowledge there are no available data on ALS's in non-cirrhotic alcohol abusers.

Conclusions

In conclusion, in non-cirrhotic subjects, regardless of hepatic enzymes' levels, alcohol detoxification had only slight effects on IGF-I and IGFBP-3. Thus, it appears that in non-cirrhotic subjects no major IGF-I/IGFBP-3 disturbances are present; apparently, in these subjects the ill-effects of chronic alcohol abuse are not mediated through IGF-I/IGFBP-3.

Conflict of interest

All the authors have no conflict of interest to declare.

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