Interrelationship of Hepatic Function, Thyroid Activity and Mood Status in Alcohol-dependent Individuals

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Abstract. Background: Alcohol-induced changes in thyroid function may contribute to the development of mood disorders such as depression and anxiety that almost invariably coexist in alcohol-dependent individuals. The aim of the present study was to investigate the severity of liver dysfunction and thyroid activity in correlation with anxiety and depressive-like symptomatology before and after a detoxification period.

Patients and Methods: In a sample of 100 alcohol-abusing/dependent subjects treated on an in-patient basis according to a standard detoxification protocol, measurements of the serum levels of hepatic enzymes (ASAT, ALAT, yGT) and thyroid hormones (T3, T4, TSH) as well as measures of anxiety, depression and global functioning were obtained at baseline and at weekly intervals over the period of 4-5 weeks.

Results: After completion of the alcohol detoxification, most measurements returned to normal levels and correlations were observed between the levels of hepatic enzymes and thyroid hormones. Additionally, a significant correlation was obtained between the levels of thyroid hormones and the mood status scales.

Conclusion: Our results indicated a dysfunction of the hypothalamic-pituitary-thyroid axis in alcohol dependence with possible implications in the diagnosis and treatment of mood disorders associated with alcohol abuse.

Alcohol abuse/dependence represents a serious health issue with major socio-economic consequences. It has been estimated that 20-50% of alcohol-dependent individuals are receiving medical care, whereas the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) describes alcohol as the most frequently used brain depressant in most cultures and a cause of considerable morbidity and mortality (1, 2).

Although various biological and psychochemical factors may contribute to the etiology and pathogenesis of alcohol dependence (3, 4), it has been associated prominently with liver disease (5, 6) and thyroid dysfunction (7, 8).

Alcoholic liver disease remains one of the most common causes of chronic liver disease in the world, usually accompanied by hepatitis, cirrhosis and/or hepatocellular cancer (9). The severity of liver dysfunction related to alcohol varies among different individuals and even within any given individual at different times. It has been estimated that only 30% of alcohol-abusing subjects develop cirrhosis, suggesting that the development of alcohol-induced liver injury requires one or more additional factors (10). Alcohol-induced liver damage as well as the associated tissue injury are commonly assessed by the levels of hepatic enzymes ASAT (aspartate-aminotransferase), ALAT (alanine-aminotransferase) and yGT (gamma-glutamyl transpeptidase) (11-14).

Furthermore, alcohol abuse frequently produces modest reductions in serum thyroxine (T4) levels and more considerable reductions in triiodothyronine (T3) levels (15). In addition, many alcohol-dependent individuals present a ‘euthyroid sick syndrome’, evidenced by low levels of T3, high levels of rT3 and normal levels of T4 (16). Many alcohol-abusing subjects have an increased binding capacity of thyroid hormones, evidenced by a decreased T3 uptake value and an increased level of thyroxin-binding globulin. A blunted thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH) administration is the most characteristic abnormality of the thyroid function in alcohol dependence (17). Thyroid
abnormalities in alcohol-dependent individuals can possibly reflect the influence of liver disease. However, no association between liver damage and thyroid function has been established.

Thyroid dysfunction has previously been associated with the severity of withdrawal and negative mood states and can be associated with an increased relapse risk in alcohol abuse (18). Clinically, a blunted TSH response in the TRH-test has been shown to be correlated linearly with an earlier onset of alcohol-dependence and a short remission in the past may be an important relapse predictor among alcohol-dependent subjects (19). During the early abstinence period, peripheral thyroid function parameters have been reported to be reduced and may reflect a subclinical hypothyroidism. However, the findings and interpretation of thyroid deregulation in alcohol abuse remain controversial. While some authors have suggested specific and partly contradicting hypotheses on the causes and consequences of the observed modifications, the majority of studies have remained descriptive.

The aim of the present study was initially to investigate the possible direct effects of alcohol abuse on the thyroid gland, dependent or not on liver damage and, further to show how these effects correlate with the development of mood disorders in alcohol-dependent individuals. For this purpose, an analysis was performed on the common hepatic markers and thyroid hormones in correlation with the mood status in a panel of 100 alcohol-dependent individuals consecutively admitted to our department for detoxification.

Patients and Methods

Subjects. The study sample comprised 100 alcohol-dependent individuals (81 males and 19 females), enrolled over a one-year period, who had consecutively contacted the Drug and Alcohol Addiction Clinic of the Egiontio University Hospital in Athens, Greece. All patients who fulfilled the DSM-IV diagnostic criteria for alcohol-abuse/dependent-“primary alcoholism” (1) were admitted to this specialized department for alcohol detoxification on an in-patient basis. The patients had abstained from alcohol for an average of 24.0±12.2 hours prior to their admission to the clinic. Informed consent was obtained from each individual, and participation in the project was on a voluntary basis. Detailed information on the objectives of the study and the research therapeutic protocol was provided to all subjects. Ethical permission for the study was obtained from the special scientific committee of the hospital and the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983.

The average alcohol intake had been higher than >270 g per day for a minimum of 5 years in all cases. The study subjects had to fulfill the following criteria: (i) age between 22 -76 years old; (ii) absence of serious physical illness (as assessed through physical examination and routine laboratory screening); (iii) absence of another pre- or coexisting major psychiatric disorder on the DSM-IV axis I; (iv) absence of another drug abuse; and (v) the mere presence of affective symptoms was not considered to be an exclusion criterion. Alcohol abusers who fulfilled the DSM-IV diagnosis of depressive disorder were excluded from the study if a major depressive episode had been recorded before the beginning of alcoholism. When the depressive episode was present concurrently with an alcohol-abusing period, these patients were not excluded.

Study design. Upon admission, alcohol detoxification was initiated and completed over one week (approximately 7 to 10 days) in all subjects. Detoxification comprised vitamin replacement (vitamins of B complex, vitamin C, vitamin E) and oral administration of diazepam (10-40 mg daily in divided doses), with gradual taper off over a week. Thereafter, the participants followed a standard in-patient treatment program with a short-term psychotherapy of cognitive-behavioral orientation. This program lasted for 4-5 weeks. It consisted both of individual sessions (twice a week) and family interventions (at least once every 2 weeks). It is self-evident that alcohol consumption was prohibited during hospitalization.

Assessments. The participants were diagnosed by the Schedules for Clinical Assessment in Neuropsychiatry and assessed through the Composite International Diagnostic Interview (20) for their pattern of alcohol abuse, potential major life problems related to alcohol consumption and the occurrence of withdrawal symptoms in the past; a structured questionnaire similar to the one proposed by the World Health Organization (21) was also used to assess the pattern of alcohol use. This questionnaire includes items related to lifetime, past year and past month frequency and quantity of alcohol use. Furthermore, sociodemographic data (age, socioeconomic status, marital status, level of education) and previous psychiatric history (pre-existent diagnosis, medications and hospitalizations) were recorded (21).

The Hamilton Depression Rating Scale (HDRS) (22), the Hamilton Anxiety Rating Scale (HARS) (23) and the Global Assessment Scale (GAS) (24, 25) were used for the assessment of psychopathology. Depressive and anxiety symptoms, as well as the level of functioning, were initially evaluated within 48 hours of entering the program (first assessment at time-point 1) and sequentially assessed 7±2 days apart, over the 4- to 5-week detoxification period (fourth assessment at time-point 4).

The concentrations of serum lipids and peripheral thyroid hormones (T3, T4, TSH) were assessed on admission (8.00 - 9.00 a.m.) and after the completion of the detoxification period using Beckman Access II diagnostic kits, USA (T3: ng/ml, T4: µg/dl and TSH: µIU/ml). The levels of hepatic enzymes (ASAT, ALAT and γGT) were also measured at the beginning as well as at the end of the detoxification program using diagnostic kits from Olympus diagnostic systems, Hamburg, Germany (ASAT, ALAT, γGT; units/ L).

All data pertaining to alcohol use were self-reported. However, to ascertain the accuracy of the information, a relative was also interviewed to corroborate the current status and psychiatric history. Four appropriately trained psychiatrists, who work in this specialized service, carried out the interviews and ratings. The mean inter-rater reliability was 0.90. A different assessor, who was blind to the previous scores, conducted the evaluation each time. Biochemists and biopathologists screened the blood examinations and elaborated the findings.
For the assessment of the severity of withdrawal symptoms, a modified version of the Addiction Research Foundation Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) was used twice daily during the first week of abstinence from alcohol. This 10-item, 5-point modified scale, which we routinely use for the assessment of alcohol withdrawal symptoms, provides a measure for symptoms of autonomic hyperarousal (nausea, tremor, sweats), anxiety, agitation, perceptual (tactile, auditory, visual) disturbances, and disorientation (rated from 0=absent to 4=severe; maximum possible score=40).

Statistical analysis. For the statistical handling of data, repeated measures analysis was applied to evaluate within-subject differences in depressive symptoms, anxiety and global functioning at the different time-points and t-tests for paired samples. Correlation coefficients (Pearson’s test and regression analysis) were calculated to detect potential statistical associations between various variables related to psychopathology and the pattern of abuse. All statistical inferences are based on 2-tail probabilities. The SPSS 11.0 statistical package was used for data handling.

Results

Demographic data. The study included 100 subjects (81 males and 19 females) who completed the 4-week detoxification period (Table I). There was no statistical age difference between male (45.64±9.94) and female alcohol-dependent individuals (45.42±9.96, min. 22, max. 76). Regarding their marital status, 55 subjects (55%) were married, 24 (24%) unmarried, 20 (20%) were divorced and 1 (1%) a widow. In terms of educational level, 16% (N=16) of them had completed more than 12 years, 48% (N=48) had completed between 9 to 12 years and 36% (N=36) less than 6 years. The mean alcohol consumption in g/per day was 265.27±138.32 (min. 52 g/day, max. 730 g/day). The mean age at onset of alcohol abuse was 26.91±10.14 (min. 12, max. 71). The age at onset of alcohol use was grouped into 5 categories: <20 years [N=33 (33% of the sample)], 20-30 years [N=40 (40% of the sample)], 30-40 years [N=20 (20% of the sample)], 40-50 years [N=2 (2% of the sample)] and >50 years [N=5 (5% of the sample)]. The mean weight was 74.42±11.45 Kg (min. 49, max. 97, male: 77.11±9.83 and female: 62.94±10.96). The mean score of cigarettes was 11.40±15.84 (min. 0, max. 60, male: 11.79±16.89 and female: 9.74±10.47). Regarding the socioeconomic status of the participants, 3% (N=3) enjoyed a high socioeconomic level, 74% (N=74) belonged to a middle socioeconomic level and 23% (N=23) a low socioeconomic status.

Biochemical profile. Upon admission, all alcohol abusers presented increased levels of cholesterol (266.4±58.89 mg/dl; normal range: 140-220 mg/dl) and triglycerides, TG (208.12±90.86 mg/dl; normal range: 50-150 mg/dl), as well as elevated HDL (65.52±24.99 mg/dl; normal range:
35-65 mg/dl) and LDL cholesterols (162.87±30.76 mg/dl, normal range: <190 mg/dl, Table II). Furthermore, all subjects presented increased serum levels of ASAT (53.89±45.22 U/L), ALAT (48.67±48.45 U/L) and a marked elevation of ÁGT (168.55±239.31 U/L). The normal range for ASAT is 7-40 U/L, for ALAT 7-40 U/L and for ÁGT 7-49 U/L.

After the detoxification period most values were significantly reduced. Specifically, cholesterol levels were 236.85±38.54 (p<0.001), TG were 139.07±34.28 (p<0.001), HDL 60.42±20.13 (NS) and LDL 159.67±25.71 (NS), respectively. The hepatic enzyme levels were also reduced with the ASAT value being 31.91±12.36 (p<0.001), ALAT 30.79±13.48 (p<0.001) and ÁGT 48.97±23.63 (p<0.001), respectively (Figure 1).

There was a statistical correlation between all hepatic markers ALAT, ASAT and ÁGT on admission (ALAT-ASAT r=0.774, p<0.001; ASAT-γGT r=0.635, p<0.001; γGT - ALAT r=0.604, p<0.001) as well as at the end of treatment (ASAT-ALAT r=0.845, p<0.001; ASAT-γGT r=0.669, p<0.001; γGT -ALAT r=0.630, p<0.001).

Weight and smoking showed no statistical correlation with any of the hepatic enzymes, suggesting that the increased levels of these enzymes on admission were not due to those factors.

Thyroid profile. Peripheral thyroid hormone levels of total T3, T4 and TSH were assessed in all patients upon admission (Table III). Specifically, the T3 levels were 1.33±0.34 ng/ml (normal range: 0.76-1.70 ng/ml), the T4 levels were 8.75±1.72 mg/dl (normal range: 6.09-12.23 mg/dl) and the TSH levels were 1.73±1.38 mIU/ml (normal range: 0.34-5.60 mIU/ml); they remained at normal levels throughout the detoxification program.

However, 30 individuals among the total population tested presented a different hormonal profile. They showed increased T3 levels (1.72±0.25) followed by normal T4 (9.59±1.44) and TSH levels (1.55±0.81) upon admission. The same group presented significantly reduced values at the end of the detoxification period (T3 1.49±0.15, T4 8.87±1.46 and TSH 1.57±0.78).

In addition, significant correlations were obtained between the levels of hepatic enzymes and thyroid hormones. In particular, there was a statistically significant reverse correlation between the ALAT and T4 levels upon admission (r = -0.216, p = 0.031) and a positive correlation between the ALAT and T3 levels at the end of the detoxification period (r = 0.218, p = 0.03).

Weight and smoking showed no statistical correlation with any of the thyroid hormones, suggesting that the increased levels of these enzymes on admission were not due to those factors.

Psychopathology. Both female and male subjects presented similar profiles in terms of the psychopathological records and there was no statistically significant difference in the assessments of all scales (HDRS, HARS and GAS) for the 2 groups.
On admission, the total HDRS mean score±SD was 39.45±6.86, 34.44±9.80 for HARS and 46.30±5.06 for GAS (Table IV). These scores indicate a severe depressive symptomatology and a high level of anxiety. At the second assessment (time-point 2), all the patients had a HDRS mean score±SD of 31.35±7.11, HARS of 27.54±8.47 and GAS 56.70±5.51. At the third assessment (time-point 3), the alcohol-dependent individuals had an HDRS mean score±SD of 14.50±6.81, HARS of 14.35±7.11 and GAS 74.30±8.68. The differences between the second and the third assessment were highly significant (p<0.001). This difference persisted until the end of the study period (time-point 4), although at a lower level of statistical significance. The values at time-point 4 were within the normal range and indicated a recovery from the anxiety and depressive symptoms after completion of the detoxification period.

Correlation coefficients (Pearson’s test) were calculated to detect potential statistical associations between various variables related to psychopathology (HDRS1 → HDRS4, HARS1 → HARS4, GAS1 → GAS4 etc.) and the levels of hepatic enzymes (ASAT, ALAT, γGT). There was a statistical correlation between all the psychopathological scales upon admission of the alcohol abusers (HRDS1-HARS1, r=0.556, p<0.001; HRDS1-GAS1, r=−0.393, p<0.001; HARS1-GAS1, r=−0.584, p<0.001), as well as at the end of the detoxification program (HRDS4-HARS4, r=0.619, p<0.001; HRDS4-GAS4, r=−0.438, p<0.001; HARS4-GAS4, r=−0.485, p<0.001).

Statistically significant correlations were obtained between the levels of ASAT on admission and HRDS1 (r=−0.180, p=0.05), as well as HARS4 at the end of the detoxification period (r=−0.215, p=0.032). Also, the γGT levels at the end of the detoxification period correlated with HARS4 (r=−0.205, p=0.04).

When thyroid hormonal levels were correlated with the mood scales, a statistically important correlation was obtained between the TSH levels and HARS1 (r=0.263, p=0.008, Figure 2).

**Discussion**

Several studies have described the effect of alcohol abuse/dependence on various organ systems. However, the multifactorial nature of alcohol dependence has made evaluation of the observed alterations and of the underlying (patho) physiological regulatory mechanisms difficult, with the majority of findings and interpretations remaining controversial.

The present study employed a variety of sophisticated questionnaires and measures of demographic, socioeconomic, biochemical and psychopathological data in a sample of 100 alcohol-dependent individuals entering a 4-week detoxification program in order to assess their overall hepatic function, thyroid activity and mood status.

Important observations were made concerning the hepatic function of alcohol-dependent individuals. As has been previously described, one of the more severe consequences of alcohol abuse is alcoholic liver disease characterized by tissue injury through hepatocytic dysfunction. Mild and moderate stages of the disorder result in cell necrosis, manifested by elevated transaminase levels (enzymatic leakage into serum of ASAT and ALAT present in hepatocytes during cell death), a transient decrease in protein synthesis and a decreased conjugation of bilirubin (5).

All alcohol-dependent individuals who participated in this study presented elevated ASAT and ALAT levels as well as increased γGT on admission, which returned to normal at the end of treatment. This profile manifested an increased liver dysfunction and concomitant liver tissue injury. Our
findings also confirmed previous studies on elevated \( \gamma \)GT concentration in alcohol-abusing subjects since this enzyme is primarily influenced by drinking intensity (24). Moreover, \( \gamma \)GT was shown to be raised in all forms of liver disease and used for identification of 34-85% of those consuming excessive amounts of alcohol before organic damage manifested. Although, the lack of specificity of increased serum \( \gamma \)GT limits its use for screening purposes, its value in the follow-up of various treatment programs is well established (25). The positive correlations that were obtained between the levels of the three hepatic enzymes reflect the significance of their combined usage for the determination of alcohol-induced liver damage.

Thyroid dysfunction has been reported among the medical problems associated with chronic alcohol abuse (7, 20, 26). In the present study, the majority of our individuals (70%) presented slightly altered peripheral thyroid hormone levels at the beginning of detoxification with reduced T3 levels and normal T4 and TSH levels. This is in agreement with a couple of studies, which present modest reductions in serum T4 levels and more considerable reductions in T3 levels (7, 15). Furthermore, it has been suggested that many alcohol-dependent individuals have a ‘euthyroid sick syndrome’, evidenced by low levels of T3, high levels of reverse T3 and normal levels of T4 (26). This syndrome has been associated with liver disease and our observation of significant correlations between the hepatic enzyme ALAT and the T3 as well as T4 levels reconfirmed the possibility of interconnection. Kinetic studies have shown that decreased production of T3 may be due to the reduced activity of type I 5’ deiodinase, the enzyme that converts T4 into T3 (27, 28). It has also been proposed that many alcohol abusers with alcoholism have an increased binding capacity for thyroid hormones, evidenced by a decreased T3 uptake value and an increased level of thyroxin-binding globulin (26).

However, a significant percentage of our individuals (30%) showed increased T3 levels, accompanied by normal levels of T4 and TSH, but the former had returned to normal at the end of the detoxification period. This observation is in agreement with four previous studies where reduced T4 concentrations were accompanied by normal or elevated concentrations of T3 (29, 30). Although the reason for T3 elevation is not known, there is a possibility that alcohol dependence reflects the influence of liver disease and also of poor nutrition (26). It has been suggested that the co-occurrence of liver cirrhosis may affect the hypothalamic-pituitary-thyroid axis (HPT) dysfunction in alcohol abuse. Depending on the severity of liver cirrhosis, the transport proteins of thyroid hormones can be reduced, further affecting the levels of total T3 and T4 in those states. Since, in the present study, only total T4 (and total T3) measurements were performed rather than free T4 and T3, the possibility cannot be excluded that the T4 levels will probably be low due to decreased thyroid-binding globulin levels (TBG), since alcohol and liver function affect TBG measurements.

In addition, alcohol-dependent subjects with a long duration of alcohol abuse presented a higher level of fibrosis of the thyroid gland than subjects with a relatively short excessive alcohol intake, indicating dose-dependent damage. However, an ultrasound study of the thyroid gland in alcohol-dependent individuals with liver cirrhosis showed a significantly decreased thyroid volume compared to the control subjects (31, 32). Therefore, alcohol may have a direct effect on the thyroid gland, which can be either dependent or independent of liver damage.

Furthermore, all the alcohol abusers presented normal TSH levels, in agreement with previous studies. The plasma TSH levels were measured after stimulation with thyrotropin-releasing hormone in alcohol-dependent subjects compared to controls. A significant blunted response to TSH was observed, which correlated positively with the severity of the withdrawal symptoms (33).

The fact that our observations on thyroid function were not homogeneous for all individuals, as well as the controversial results of previous studies, confirms the complexity of alcohol-associated dysregulation in the HPT axis. In addition, the recovery of any alterations in thyroid profile during abstinence suggests that thyroid dysfunction is not a trait marker of alcohol dependence and that other endogenous or exogenous factors act in concert with alcohol intake.

Furthermore, the alcohol-dependent individuals who entered the study presented with severe depressive and anxiety symptoms such as depressive mood, sleep disorders, severe anxiety, low self-confidence, no desire to work, anorexia etc. (34-36). These symptoms are in agreement with the estimated prevalence of depressive-like symptomatology in alcohol-abusing subjects ranging from 15-70% (37) and of anxiety being 5-56% (38, 39). The Collaborative Study on the Genetics of Alcoholism (COGA) found an increased prevalence of depressive syndrome (i.e., depression that may or may not occur in conjunction with increased drinking) (25, 41). Although previous research has found a relationship between anxiety disorders and alcoholism, other studies presented contradictory results in drinking levels among socially anxious individuals, dysthymics and normal controls (42). Since alcohol abuse and dependence significantly affect the thyroid function, considerable evidence suggests that minor changes in thyroid function may affect the mood and behavior (40, 43-44). Thus, it is reasonable to suggest that alcohol-induced changes in thyroid function may make a contribution to the development of depression-like symptomatology in alcohol-dependent individuals.
Furthermore, this study presented a correlation between the levels of TSH and increased anxiety symptoms at the beginning of the detoxification program, probably suggesting a possible mechanism of action for alcohol. Since no correlation was observed between the thyroid hormones and the depression scales, it is possible that alcohol-induced changes in thyroid function are not a sufficient cause of depression. Most probably, they work in concert with inherited, acquired and environmental risk factors.

In conclusion, the significant improvement of the psychopathological profile of the study group in correlation with amelioration of both hepatic and thyroid functions by the end of the detoxification program provide important implications for everyday clinical practice, in relation to the differential diagnosis among the primary mood disorders of the Axis I and the secondary mood disorders induced by alcohol abuse/dependence.

Future investigation of the complex interrelationships between hepatic function, thyroid activity and mood status in alcohol-dependent patients is needed in the light of other sequel of long-term heavy alcohol use such as concurrent adaptive changes, organ dysfunction or organ damage, as well as disturbance in hormonal and neurohormonal regulation.

Ensuing studies should compare the present data to controls, e.g., individuals with alcohol dependence but no liver damage, persons matched for similar anxiety/depression tests but no liver abnormalities/alcohol dependence, or individuals matched for similar liver dysfunction due to causes other than alcohol. This would help sort out whether anxiety (independently of alcohol or liver damage) contributes to the thyroid function tests found.

References


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