ERYTHROCYTE THIAMINE (Th) ESTERS: A MAJOR FACTOR OF THE ALCOHOL WITHDRAWAL SYNDROME OR A CANDIDATE MARKER FOR ALCOHOLISM ITSELF?

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Abstract — Aims: Thiamine (Th) deficiency is a major problem in alcoholics. In this study, the relationship of alcohol withdrawal syndrome (AWS) to Th and its esters, as well as the diagnostic power of Th and its esters were investigated. Patients and methods: Th and its esters were assessed in a series of chronic alcoholics (and in controls) using an improved method. Results: No association was found between AWS severity and Th and its esters, while the diagnostic power of thiamine diphosphate (TDP) and Th was very high. TDP was the most significant among the parameters under study, confirming that erythrocyte TDP is a suitable marker of alcoholism; TDP sensitivity across subjects was 84.1%, specificity 85.4%, positive predictive value 82.4%, and negative predictive value 88.0%.

INTRODUCTION

Alcohol induced impairment of thiamine (Th) absorption and Th diphosphate (TDP) synthesis (Nishino and Itokawa, 1977; Gubler, 1991) as well as decreased dietary intake of Th (Stacey and Sullivan, 2004) lead to Th deficiency (TD) in chronic alcoholics. Malnutrition in the absence of alcohol, as in subjects affected by celiac sprue, Crohn’s disease, or short bowel syndrome, can also cause malabsorption of Th. In heavy drinkers malabsorption is frequent, due to severe chronic impairment of liver or pancreas, and is a major cause of Th deficit. Indeed, Th intake is often impaired in alcoholics, mainly in homeless subjects. The effects of alcohol-dependent and alcohol-independent malnutrition are probably additive.

TD in alcoholics is a well-known problem and contributes to nervous system impairment: TDP is the coenzyme of several intra-mitochondrial enzymes, involved in carbohydrate and lipid metabolism, such as piruvate dehydrogenase (PDH), alpha ketoglutarate dehydrogenase (α-KGDH), and transketolase (TK) (Nishino and Itokawa, 1977; Gubler, 1991); α-KGDH impairment could have a key role in Wernike– Korsakow syndrome (WKS) (Nishino and Itokawa, 1977). Th-dependent enzymes are important in the biosynthesis of a number of cell constituents, including neurotransmitters, and for the production of reducing equivalents used in oxidant stress defence and in the biosynthesis of pentoses, nucleic acid precursors (Butterworth, 1993; Pannunzio et al., 2000; Thomson, 2000; Lee et al., 2001; Singleton and Martin, 2001). TD has been implicated in central and peripheral WKS, in alcoholism-induced cognitive deficit and in alcohol peripheral neuropathies (Butterworth, 1993; Cook et al., 1998; Pannunzio et al., 2000; Thomson, 2000; Lee et al., 2001; Singleton and Martin, 2001). Glycerophosphorylcholine (GPC) depletion, triggered by TD, may be the primary biochemical lesion leading to WKS (Pannunzio et al., 2000); other issues related to TD in alcoholics remain even further from resolution [e.g. in a group of heavy drinkers abnormally low TK protein activity was found, thus suggesting that (Butterworth, 1993; Panunzio et al., 2000; Thomson, 2000; Lee et al., 2001; Singleton and Martin, 2001) impaired Th utilization might lead to more severe brain damage in a specific subgroup of patients (Heap et al., 2002)]. Experimental data suggest that TK activity, as well as the activity of other Th-utilizing enzymes, may be downregulated in TD (Butterworth, 1993; Pekovich et al., 1998; Heap et al., 2002). Also Th phosphorylation (especially synthesis and accumulation of TDP) is impaired in alcoholics, mainly in the liver, as only Th and not its phosphates can easily cross hepatocyte membranes (Fig. 1) (Yoshioka et al., 1983; Rindi et al., 1992).

In an earlier study (Mancinelli et al., 2003) our group carefully assessed Th status in a series of chronic alcoholics, by evaluating the erythrocyte levels of Th and its esters, Th monophosphate (TMP) and TDP. Simply assessing serum Th in isolation is not advisable, since the sensitivity and specificity of Th are rather low and most of the Th resides in the erythrocytes, in esterified form. In this investigation erythrocyte TDP and, to a minor extent, Th levels were

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significantly lower (P < 10⁻⁵) in alcoholics than in controls. Such a striking significance is very rare in alcoholism studies, where delineations between chronic alcoholics, occasional heavy drinkers, alcohol abusers, and social drinkers are somewhat blurred, and significance levels for candidate markers of alcoholism are often low (Ewing, 1984; Hillman et al., 1998; Schmitt et al., 1997; 1998; Sharpe, 2001).

In this study, erythrocyte TDP, as well as Th and TMP were assessed in a larger series of alcoholics, to determine whether erythrocyte TDP might serve as a useful marker of alcoholism. A puzzling problem is the role of TD in the pathogenesis of the alcohol withdrawal syndrome (AWS). High-dose Th administration is a mainstay of the AWS treatment in clinical settings (Schuckit, 2005), along with benzodiazepines (BDZs), but this is an empirical treatment, since the role of Th deficit in AWS is poorly understood and conflicting results have been reported (e.g. in alcoholics affected by delirium tremens, the most dangerous outcome of AWS, serum Th was lower than in uncomplicated alcoholics (Hoes, 1981)) while no difference was found for erythrocyte TK activity, a sensitive indicator of Th level, between alcoholics with severe AWS and controls (Nordentoft et al., 1993; Heap et al., 2002).

In the present study, erythrocyte Th, TMP, and TDP levels were assessed to:

- • Further explore their diagnostic values.
- • Investigate their relationship — if any — with AWS severity levels, in order to establish a less empirical indication for Th treatment in AWS.

Secondary aims were to investigate erythrocyte Th, TMP, and TDP relationship — if any — with alcohol intake and with other significant biochemical markers.

PATIENTS AND METHODS

Patients

Alcoholics. The subjects enrolled in this study consecutively entered the Alcohol Liver Disease Unit (University ‘La Sapienza’, Rome), where they were treated in day-hospital for ~14 days (8.00 a.m. to 1.00 p.m.). The diagnosis of chronic alcoholism was established according to DSM IV criteria (DSM-IV, 1994) and 82 adult subjects, 62 male and 20 female, were enrolled. Patients below or above 20–75 y age were excluded from the study as were individuals affected by severe diseases (such as cancer or AIDS), by acute alcoholic hepatitis, by alcohol-independent malabsorption syndromes, or by Child–Pugh (Pugh et al., 1973) C liver cirrhosis. Fifteen patients (12 male, 3 female) were affected by liver cirrhosis (10 by Child–Pugh A, 5 by Child–Pugh B). Sixty-seven were affected by alcoholic liver steatosis. In most patients, the diagnosis of liver steatosis or cirrhosis was informed by clinical signs and laboratory results, as liver biopsy is not routinely performed in day-hospital patients in Italy. No patient had signs or symptoms of acute viral hepatitis or was on pharmacological treatment for viral hepatitis. Subjects affected by co-dependence (alcohol and a different addictive molecule) were not included in this study.

Subject characteristics are reported in Table 1 and occupations in Table 2. A detailed medical history was obtained using the Lifetime Drinking History instrument (LDH) (Skinner and

<table>
<thead>
<tr>
<th>Statistics and alcohol intake</th>
<th>Alcoholics (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>42.01 ± 11.62</td>
</tr>
<tr>
<td>At risk alcohol intake (y)</td>
<td>20.57 ± 12.22</td>
</tr>
<tr>
<td>Last year alcohol intake (mean drinks/day)</td>
<td>14.52 ± 8.75</td>
</tr>
<tr>
<td>Last month alcohol intake (mean drinks/day)</td>
<td>14.90 ± 9.02</td>
</tr>
<tr>
<td>Age of onset of at-risk drinking (yrs.)</td>
<td>21.44 ± 7.69</td>
</tr>
<tr>
<td>Days from last drink</td>
<td>2.01 ± 2.08</td>
</tr>
<tr>
<td>AWSb</td>
<td>4.57 ± 1.14</td>
</tr>
<tr>
<td>CIWA-ar</td>
<td>5.85 ± 3.80</td>
</tr>
</tbody>
</table>

*Drink: about 13 g of alcohol.
*Lifelong number of AWS episodes.

Table 2. Occupation of the patients

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Percent values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worker</td>
<td>25.0</td>
</tr>
<tr>
<td>Clerk</td>
<td>16.3</td>
</tr>
<tr>
<td>Professional</td>
<td>8.8</td>
</tr>
<tr>
<td>Housewife</td>
<td>7.5</td>
</tr>
<tr>
<td>Retired</td>
<td>10.0</td>
</tr>
<tr>
<td>Unemployed</td>
<td>32.5</td>
</tr>
</tbody>
</table>

Sheu, 1982), detailing the years of high-risk consumption, i.e. daily alcohol consumption >25 g for females, and 40 g for males at risk for the onset of alcohol-related pathologies (WHO, 2000). Amount of alcohol consumption — lifelong and during the last year — was estimated by the LDH. Intake during the preceding month was estimated by the Alcohol Timeline Followback (TLFB) (Sobell and Sobell, 1955). Previous episodes of AWS were carefully recorded. Self-reported occasional consumption of illegal psycho-active substances was investigated since in the last decades alcohol addiction has often been found in association with the use of other psycho-active drugs (Martin et al., 1993). Physical examination was performed and body mass index (BMI) was calculated. Blood alcohol concentration (BAC) was assessed daily by breath-test (Pocket Alcolmeter Lion SD 400, MORGAN Italy) and TLFB was performed. AWS symptoms (tremors of the hands, agitation, etc.) were carefully investigated and AWS severity was assessed by Clinical Institute Withdrawal Assessment for Alcohol (CIWA-ar) test (Sullivan et al., 1989) a structured questionnaire based on the semi-quantitative evaluation of the main symptoms of AWS. The highest CIWA-ar value found during the hospitalization was taken into account for statistics. BDZs were administered if the CIWA-ar score exceeded 10. None of the patients showed signs suggestive of WKS, like confusion, either in the whole series, or in the AWS subset: maybe the careful check-up of AWS symptoms, and the precocious administration of BDZs, prevented the onset of WKS in AWS subjects (Victor et al., 1989).

Control subjects were randomly drawn from healthy subjects attending the ‘Prevention and Work Security Service’ for routine medical examination. All had haematological and biochemical parameters within reference range and no significant medical history. No subject was on restricted or abnormal diet. One hundred and thirteen controls (mean age 42.94 ± 10.17 y), 45 males (45.8 ± 0.2) and 58 females (40.22 ± 9), were included in the study.
No subject under study (alcoholics or controls) had received vitamin supplementation before the blood draw. Informed consent was obtained from all the subjects enrolled in this study.

**Samples**

The blood samples employed for this study were taken on the first day in day-hospital. Samples were coded to guarantee personal privacy.

**Methods**

**Assessment of Th and its esters.** Blood samples (7 ml) were collected after overnight fasting in EDTA or heparin vacutainers on the first day of hospitalization. Erythrocytes were separated by centrifugation, washed in saline solution, and haemolysed. The improved method for the assessment of Th and its esters by HPLC fluorimetric detection is detailed elsewhere (Mancinelli et al., 2003). HBV and HCV markers were assessed in all the patients by ELISA and third generation RIBA tests. HCV-RNA was evaluated in patients with anti-HCV antibodies.

**Statistical analyses.** The significance of differences between groups was calculated by the Mann–Whitney $U$-test. Correlation significance was assessed by the Spearman’s rho correlation coefficient. Three different Receiver Operating Characteristic (ROC) curves were calculated for Th, TMP, and TDP values. Three levels of sensitivity, specificity, and predictive values were calculated [95% confidence intervals (CI)] for different clinical purposes. To investigate relationships between the levels of Th and its esters and the AWS symptoms (assessed by the CIW A-ar test) and the biochemical tests, an analysis of variance ANOVA (one-way) with post hoc Bonferroni correction was performed on normalized data by ln-transformation. The one-sample Kolmogorov–Smirnov (K–S) procedure was used to test the null hypothesis that neither group had normal distributions $(P < 0.0005)$ for TMP only. The two-sample K–S tests between alcoholics and controls distribution were highly significant for TDP $(P < 0.0005)$ and Th $(P < 0.0005)$ but not significant for TMP.

A highly significant difference between alcoholics (59.59 ± 25.68 nmol/l) and controls (89.60 ± 22.70 nmol/l) was found on the Th assay $(P < 10^{-5})$ (Table 4). No significant difference between the mean values for alcoholics (2.64 ± 3.35 nmol/l) and for controls (4.21 ± 6.37 nmol/l) was found on the TMP assay (Table 4). The mean values for alcoholics on the TDP assay (123.78 ± 43.68 nmol/l) were significantly different from mean values for controls (222.24 ± 54.56 nmol/l): $P < 10^{-5}$ (Table 4). No significant difference was found between cirrhosis group $(n = 15)$ and the whole group of alcoholics (Table 4). ROC curves for Th, TMP, and TDP values were calculated for all subjects (Fig. 2), for males and females separately (Figs 3 and 4). For TDP, sensitivity across subjects was 84.1%, specificity 85.4%, positive predictive value 82.4%, and negative predictive value 88.0% (Table 5 and Fig. 2). Also a striking significant gender difference (Figs 3 and 4) was found $(P < 0.0005)$. Areas under the curves (AUC) were also calculated (Table 6), creating multiple curves in order to compare three competing classification models. In the whole sample, the best models are TDP and Th, while for TMP the entirety interval lies below the others.

**RESULTS**

Descriptive statistics and alcohol intake parameters are reported in Tables 1 and 2. On average, excess alcohol intake lasted for $20.57 ± 12.22$ y with a tendency towards a gender effect $(P = 0.075)$ with males being at $22.71 ± 11.87$ y and females at $13.95 ± 11.12$ y. For age of onset at-risk consumption, a gender difference was found: females, $24.85 ± 10.21$ y; males, $20.33 ± 6.41$ y, $P < 0.005$. The preceding month’s alcohol intake was $14.90 ± 9.02$ drinks/day.

Biochemical markers yielding pathological results and gender differences are reported in Table 3. Significant gender differences were observed for ALT $(P = 0.03)$, and ferritin $(P = 0.04)$ and a tendency towards significance $(P = 0.06)$ was observed for γGT.

As noted, the one-sample K–S procedure was used to test the null hypothesis that neither group had normal distributions on scores related to Th. The test was significant $(P < 0.0005)$ for TMP only. The two-sample K–S tests between alcoholics and controls distribution were highly significant for TDP $(P < 0.0005)$ and Th $(P < 0.0005)$ but not significant for TMP.

The statistical level for evaluating results was set at $P = 0.05$. The statistical package SPSS 11.0 for Windows was employed.

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### Table 3. Routine biochemical tests (mean ± SD)

<table>
<thead>
<tr>
<th>Test (reference values)</th>
<th>Alcoholics $(n = 82)$</th>
<th>Gender differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>γGT (10–49 U/l)</td>
<td>232.66 ± 597.96</td>
<td>$P = 0.06$</td>
</tr>
<tr>
<td>AST (10–37 U/l)</td>
<td>82.13 ± 81.83</td>
<td>$P = 0.08$</td>
</tr>
<tr>
<td>ALT (10–37 U/l)</td>
<td>51.46 ± 40.45</td>
<td>$P = 0.03$</td>
</tr>
<tr>
<td>MCV (82–96 fl)</td>
<td>95.88 ± 8.35</td>
<td>$P = 0.56$</td>
</tr>
<tr>
<td>Total bilirubin (0–1.1 mg/dl)</td>
<td>0.73 ± 0.40</td>
<td>$P = 0.38$</td>
</tr>
<tr>
<td>Ferritin (20–300 ng/dl)</td>
<td>157.06 ± 39.38</td>
<td>$P = 0.04$</td>
</tr>
</tbody>
</table>

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### Table 4. Thiamin and its esters in alcoholics (cirrhosis and others) and in controls (mean ± SD, nmol/l)

<table>
<thead>
<tr>
<th></th>
<th>Alcoholics</th>
<th>Controls</th>
<th>$P^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All$^a$</td>
<td>Cirrhosis</td>
<td>Others</td>
</tr>
<tr>
<td>Thiamin</td>
<td>59.59 ± 25.68</td>
<td>64.38 ± 17.55</td>
<td>60.13 ± 27.00</td>
</tr>
<tr>
<td>TMP</td>
<td>2.64 ± 3.35</td>
<td>3.11 ± 4.14</td>
<td>2.64 ± 3.34</td>
</tr>
<tr>
<td>TDP</td>
<td>123.78 ± 43.68</td>
<td>108.07 ± 31.57</td>
<td>128.39 ± 50.09</td>
</tr>
</tbody>
</table>

n.s.: not significant.

$^a$All: all the alcoholics on study.

$^b$Significance of differences, all alcoholics vs controls.
If the sample is split into males and females, the results are very similar, but Th seems slightly better than TDP in females. Partial correlations were calculated, controlling for age, BMI, years of at-risk alcohol intake and last month alcohol intake (drinks/day) (Table 7): Th was correlated to AST ($P < 0.01$), ALT ($P < 0.001$), and MCV ($P < 0.02$); TMP was correlated to AST ($P < 0.03$) and ALT ($P < 0.01$). There were no correlations found with TDP.

The ANOVA using CIWA-ar values and the number of AWS episodes as the dependent variables and Th and its esters as independent variables failed to show a significant effect. Among the alcoholics under study, 15 were positive for HCV-RNA and four were positive for HBsAg. No significant differences were found between the HCV-RNA positive patients and the other alcoholics under study.

Self-reported occasional consumption of illegal drugs is reported in Table 8. No significant difference was found between the alcoholics using illegal drugs and the others. A biochemical assessment of nutritional status was performed. Albumin and BMI values were within normal limits, while the levels of ferritin and lymphocytes (Table 9) suggested a status of mild malnutrition (Blackburn et al., 1977).

**DISCUSSION**

In this study, the highly significant difference between alcoholics and controls for erythrocyte TDP and Th values was fully confirmed. Indeed, the ROC curves of males and females (Figs 3 and 4) were different. This result is difficult to explain since there is no known effect of sex hormones on these parameters. The findings may reflect years of at-risk alcohol consumption (significantly higher in males) and age of onset (significantly greater in females). In our series, women started drinking heavily later and abused alcohol for a shorter time, without any gender difference for drinking severity or for stage of alcoholic liver disease. The so-called 'telescoping effect' [i.e. accelerated progression towards alcohol dependence (Haas and Peters, 2000) and towards severe alcohol liver disease] suggests that women are more vulnerable than...
Table 8. Alcoholics taking illegal drugs in the last 6 months (present) and before the last 6 months (past)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Present (%)</th>
<th>Past (%)</th>
<th>Males (%)</th>
<th>Females (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin</td>
<td>7.3</td>
<td>17.7</td>
<td>5.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Cocaine</td>
<td>13.9</td>
<td>36.7</td>
<td>13.3</td>
<td>35.0</td>
</tr>
<tr>
<td>THC</td>
<td>8.9</td>
<td>29.1</td>
<td>20.0</td>
<td>28.3</td>
</tr>
</tbody>
</table>

All, all the alcoholics on study; M, males; F, females.

Men to alcoholic damage. Unfortunately, the number of females in our series of alcoholics was small, and further research in larger series is needed. The female group should be split into subsets of fertile and infertile subjects to assess the effects (if any) of sexual hormones.

No significant difference was found for Th or its esters between patients consuming alcohol only and patients consuming illicit drugs occasionally. Further exploration of this topic, as well as of the gender differences found in this study, would prove fruitful.

No significant and reliable positive correlation was found between Th and its esters and the lifelong amount of AWS intake, last month alcohol intake.

In the assessment of body composition is a debated matter, mainly when modifications of total body water are crucial, as in alcoholics. Our data may be biased by water retention, common in heavily drinking alcoholics (like most of our patients), since the assessment of body weight (BMI: body weight/body height²) cannot distinguish between fat, muscle, or water. Indeed, only a few patients under study were homeless or very low-income subjects. Most held a regular job and maintained a good income and, therefore, poverty-related starvation (often the cause of malnutrition in alcoholics) can be dismissed in our series. Further, unemployed (32% of our series) and even homeless patients were assisted by public or private charities. Lymphocyte depletion could be an early-stage finding of alcoholism malnutrition, or rather might be related to alcohol-induced impairment of the immune system. Further research is needed.

Significant partial correlations were found between Th and TMP and some commonly used markers of alcoholism, MCV, AST, and ALT. No correlation was found for TDP, the active form of Th, and γGT, the more popular marker of alcoholism.

Considering the striking significance of TDP decrease in alcoholics, erythrocyte TDP could be proposed as a new candidate marker of alcoholism. In our opinion, since alcoholism is extremely prevalent in many countries procedures designed to allow early diagnosis are needed. A reliable marker of alcoholism could be very helpful for the diagnosis, but none of the established markers is adequate in its own right to support the diagnosis of alcoholism (Ewing et al., 1984; Schuckit et al., 1994; Hillman et al., 1998; Schmitt et al., 1998; Allen et al., 2000; Bean et al., 2001; Sharpe, 2001; Sass et al., 2004).

Diagnosis of alcoholism in non-compliant subjects may be informed by clinical interview, physical signs of alcohol intake or alcohol-related physical damage (Sharpe, 2001), self-reported screening measures, (Nilssen and Forde, 1991; Schuckit et al., 1994; Stockwell et al., 1994; Storgaard et al., 1994) and biomarkers of heavy drinking (Cohen and Kaplan, 1979; Ewing, 1984; Orrego et al., 1985; Conigrave et al., 1994).
Table 9. Nutritional assessment

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Under study</th>
<th>Normal</th>
<th>Mild malnutrition</th>
<th>Moderate malnutrition</th>
<th>Severe malnutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>24.4 ± 0.5</td>
<td>18.5–24.9</td>
<td>17–18.4</td>
<td>16–16.9</td>
<td>&lt;16.0</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.6 ± 90.0</td>
<td>&gt;3.5 g/dl</td>
<td>3.5–2.8</td>
<td>3.5–2.1</td>
<td>&lt;2.1</td>
</tr>
<tr>
<td>Ferritin</td>
<td>157.1 ± 29.1</td>
<td>&gt;200 mcg/l</td>
<td>151–200</td>
<td>100–150</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1880.5 ± 896.0</td>
<td>&gt;2000/mm³</td>
<td>1200–2000</td>
<td>800–1000</td>
<td>&lt;800</td>
</tr>
</tbody>
</table>

procedure (Mancinelli et al., 2003). The cost/benefit ratio, in terms of better clinical management of the patient, argues for wider use of TDP and Th in studies on alcoholism and nutritional impairment. This marker may assist early diagnosis in difficult cases when other biological markers do not yield a reliable answer. The diagnostic power of TDP assessment is high (Sgouros et al., 2004). We have found a sensitivity value of 85% and a specificity of 84%. This finding may be somewhat biased (spectrum bias), as contrasting two extreme groups will over-estimate test sensitivity and/or specificity (Lijmer et al., 1999): thus, further research is needed in non-extreme groups, as moderate drinkers, adolescent drinkers, etc. As Th deficiency may be caused by a number of other conditions occurring separately from alcohol misuse (celiac sprue, Crohn’s disease, short bowel syndrome, etc.) (Levy et al., 1965; Thomson et al., 2002) or in conjunction with it, all of them have to be excluded in any patient, a simple task in most cases. Moreover, the low levels of Th and its esters could be related to liver disease, rather than to alcohol dependence: this could be a debated point for alcoholic cirrhosis, since low levels of Th were found in HCV cirrhosis (Levy et al., 2002), but not in non-alcoholic liver steatosis.

In conclusion, the values of Th and TDP were not correlated to CIWA-ar values or to levels of alcohol intake, while the diagnostic power of Th and TDP was fully confirmed. TDP seems a marker independent of the common markers of alcoholism, as it is not correlated to γGT and is weakly correlated to AST, ALT, and MCV. The hypothesis that TDP may be a reliable marker of alcoholism is supported by our findings.

REFERENCES


