Carbohydrate-deficient transferrin and gamma-glutamyl transpeptidase in the evaluation of alcohol consumption

A five-year retrospective study of 633 outpatients in a single center

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SUMMARY

Objective — Carbohydrate-deficient transferrin has been proposed to be useful in evaluating alcohol consumption but there is no consensus on its use in routine practice. The aim of this retrospective study was to compare carbohydrate-deficient transferrin and gamma-glutamyl transpeptidase assays for the evaluation of alcohol consumption.

Methods — Six hundred thirty-three outpatients attending one outpatient care center were included in this study. Patients were divided into five categories according to alcohol consumption: category 1 included non-weaned patients drinking more than 30 g/day for women and more than 50 g/day for men, category 2 included relapse patients, category 3 included moderate drinkers, category 4 included patients weaned less than one month, and category 5 included patients weaned more than one month. One experienced physician estimated alcohol intake from patient declarations during a face-to-face interview.

Results — Sensitivity of carbohydrate-deficient transferrin varied, depending on patient category, from 32% to 92% versus 41% to 72% for gamma-glutamyl transpeptidase. Specificity of carbohydrate-deficient transferrin varied from 71% to 96% versus 23% to 62% for gamma-glutamyl transpeptidase. After one month of abstinence, specificity of carbohydrate-deficient transferrin was 62% versus 19% for gamma-glutamyl transpeptidase.

Conclusion — This study confirms that carbohydrate-deficient transferrin is more accurate in predicting alcohol consumption compared with gamma-glutamyl transpeptidase in alcoholic outpatients.

RéSUMÉ

Comparaison de la carbohydrate-deficient transferrine et de la gammaglutamyl transpeptidase dans l’évaluation de la consommation d’alcool. Étude rétrospective de 633 malades suivis durant une période de 5 ans dans un centre de cure ambulatoire en alcoologie

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Objectif — La place de la carbohydrate-deficient transferrine dans l’évaluation de la consommation d’alcool a par rapport aux autres marqueurs n’est pas clairement établie.

Le but de cette étude rétrospective était de comparer la carbohydrate-deficient transferrine et la gammaglutamyl transpeptidase chez des malades suivis dans un centre de cure ambulatoire en alcoologie.

Méthodes — Les 633 malades inclus dans cette étude étaient classés selon 5 statuts : statut 1 : malades non sevrés consommant plus de 30 g/j d’alcool pour les femmes et plus de 50 g/j pour les hommes, statut 2 : malades présentant une rechute, statut 3 : malades tempérants, statut 4 : malades sevrés depuis moins d’un mois, statut 5 : malades sevrés depuis plus d’un mois. Un malade pouvait appartenir à plusieurs statuts mais un seul prélèvement a été retenu par statut, soit un total de 993 prélèvements. La consommation déclarée d’alcool a été évaluée par le même médecin lors d’un entretien en face-à-face.

Résultats — Selon le statut, la sensibilité de la carbohydrate-deficient transferrine variait de 32 à 92 % et celle de la gammaglutamyl transpeptidase de 41 à 72 %. La spécificité de la carbohydrate-deficient transferrine variait de 71 à 96 % et celle de la gammaglutamyl transpeptidase de 23 à 62 %. La spécificité de la carbohydrate-deficient transferrine était de 62 % après 1 mois de sevrage alors qu’elle était de 19 % pour la gammaglutamyl transpeptidase.

Conclusion — Cette étude confirme la meilleure valeur informationnelle de la carbohydrate-deficient transferrine par rapport à la gammaglutamyl transpeptidase, pour évaluer la consommation d’alcool chez des malades alcooliques suivis en ambulatoire.

Introduction

Declared alcohol consumption, standardized questionnaires and biological markers are three methods used to evaluate alcohol consumption. Mean corpuscular volume (MCV) and serum gamma-glutamyl transpeptidase (GGT) are the most widely used biological markers [1]. In 1976, Stibler et al. [2] reported a transferrin glycosylation abnormality observed in the cerebrospinal fluid of alcoholic patients presenting neurological disorders.

This abnormality was found in the serum of alcoholic subjects without neuropathy and disappeared after 10 to 14 days of abstinence [3]. The glycosylation deficient fractions were termed carbohydrate-deficient transferrin (CDT) which has been proposed as a biological marker of alcohol consumption. Assays in different studies have demonstrated the good specificity and sensitivity of this marker [4-6]. The role of CDT in relation to other routinely used biological markers remains to be clearly established. The usefulness of CDT has not been assessed in an outpatient setting in a large number of subjects.

The purpose of this work was to examine the diagnostic value of serum CDT level in comparison with serum GGT in the assessment of alcohol intake in patients followed in an outpatient care center.
Patients and methods

Patients

From December 1996 to January 2002, 633 patients followed at the Ambulatory Care Center for Alcoholics of Tours were included in this study. There were 499 men (mean age 42 ± 10 years) and 134 women (mean age 45 ± 10 years). Most of the patients were referred to the center by general practitioners, but patients were also referred by social services, courts, or hospitals. Most of the patients did not present clinical or biological signs of severe liver disease.

Estimation of alcohol intake and patient classification

Declared alcohol consumption was evaluated by one physician (LM) specialized in alcoholology during a face-to-face interview. Five categories of patients were defined.

- Category 1: non-weaned, alcohol intake > 30 g/d for men and > 50 g/d for women,
- Category 2: relapse, alcohol intake > 30 g/d for women and > 50 g/d for men,
- Category 3: moderate drinkers, alcohol intake < 30 g/d for women and < 50 g/d for men,
- Category 4: weaned for less than one month,
- Category 5: weaned for more than one month.

When more than one blood sample was drawn when a patient was in a given category, only one sample was retained for analysis. The category of a patient could change during the course of the study. For the 633 patients included in the study, more than one blood sample was available for 223 who had sampling when in different categories. We thus retained for analysis 993 blood samples.

Assay of carbohydrate-deficient transferrin and gamma-glutamyl transpeptidase

Blood samples were drawn at the alcohol-cure outpatient center. Samples were drawn at the first consultation and later as prescribed depending on the clinical situation (change in drinking behavior, weaning).

For CDT assay, micro-column ion-exchange chromatography was used to separate the different forms of transferrin followed by nephelometric quantification [7]. Results were expressed in absolute value. The normal serum concentration of CDT for our laboratory was ≤ 60 mg/L [8].

Serum GGT activity was measured at 30°C. The laboratory normal values depended on age and gender.

Analysis of assay results

We calculated the sensitivity of serum CDT and GGT assays in patients in category 1 (non-weaned), category 2 (relapse), and category 3 (moderate drinkers) and the specificity of the assays in patients in category 4 (weaned < 1 month) and category 5 (weaned > 1 month). Sensitivity and specificity values were determined for the entire cohort and by 10-year age group. The threshold level to calculate serum CDT assay sensitivity and specificity was set at 60 mg/L.

We also studied changes in the levels of the two markers associated with weaning or relapse. For weaning, we analyzed the results obtained for 42 patients in category 1 who were later classified in category 4 (weaned < 1 month). Patients in category 4 were divided into three subgroups according to weaning time: < 11 days, 11-20 days, 21-30 days. We also analyzed results in 53 patients in category 4 who were later classified in category 5 (weaned > 1 month). For relapse, we analyzed results in 47 patients in category 5 who were later classified in category 2 (relapse).

Serum CDT and GGT levels were expressed as mean and standard deviation. Values were compared with the Mann-Whitney test for non-paired series or with the non-parametric Wilcoxon test for paired series as appropriate. P < 0.05 was considered statistically significant.

Table I. – Serum CDT and serum GGT levels according to patient category.

<table>
<thead>
<tr>
<th>Category</th>
<th>n*</th>
<th>CDT (mg/L)</th>
<th>GGT (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1 (non-weaned)</td>
<td>389</td>
<td>118 ± 60a</td>
<td>131 ± 213a</td>
</tr>
<tr>
<td>Category 2 (relapse)</td>
<td>98</td>
<td>105 ± 58</td>
<td>143 ± 481</td>
</tr>
<tr>
<td>Category 3 (moderate drinkers)</td>
<td>146</td>
<td>55 ± 2b</td>
<td>51 ± 18b</td>
</tr>
<tr>
<td>Category 4 (weaned &lt; 1 month)</td>
<td>113</td>
<td>57 ± 26c</td>
<td>154 ± 226d</td>
</tr>
<tr>
<td>Category 5 (weaned &gt; 1 month)</td>
<td>247</td>
<td>43 ± 11*</td>
<td>45 ± 72*</td>
</tr>
</tbody>
</table>

* n: number of samples; a P < 0.001 compared with categories 2, 3, 4 and 5; b P < 0.001 compared with category 2; c P < 0.005 compared with categories 1 and 2; d P < 0.05 compared with categories 1, 2, 3 and 5; e P < 0.001 compared with categories 1, 2, 3 and 4.

Results

Serum CDT and GGT levels are presented in table I as a function of alcohol intake. Serum CDT level was higher in patients in category 1 (non-weaned) than in patients in the other categories (P < 0.001). However, serum GGT levels were lower in patients in category 1 compared with patients in category 2 (relapse) and category 4 (weaned < 1 month) (P < 0.001).

The sensitivity of the assays for the two markers are presented in table II for patients in categories 1 (non-weaned), 2 (relapse), and 3 (moderate drinkers). Specificity values for the two markers are presented in table III for patients in categories 4 (weaned < 1 month) and 5 (weaned > 1 month). Considering all samples, the positive predictive value of CDT was 92%; its negative predictive value was 70%. The positive predictive value of GGT was 68% and its negative predictive value was 42%.

Table II. – Sensitivity of CDT and GGT in patients in category 1 (non-weaned), category 2 (relapse), and category 3 (moderate drinkers) according to age group.

<table>
<thead>
<tr>
<th>Category</th>
<th>Age group (years)</th>
<th>n*</th>
<th>CDT</th>
<th>GGT</th>
<th>n*</th>
<th>CDT</th>
<th>GGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>≤ 29</td>
<td>30</td>
<td>100%</td>
<td>70%</td>
<td>7</td>
<td>71%</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>30-39</td>
<td>115</td>
<td>95%</td>
<td>63%</td>
<td>20</td>
<td>100%</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td>40-49</td>
<td>164</td>
<td>90%</td>
<td>73%</td>
<td>40</td>
<td>88%</td>
<td>53%</td>
</tr>
<tr>
<td></td>
<td>50-59</td>
<td>68</td>
<td>87%</td>
<td>81%</td>
<td>19</td>
<td>79%</td>
<td>63%</td>
</tr>
<tr>
<td></td>
<td>≥ 60</td>
<td>12</td>
<td>83%</td>
<td>75%</td>
<td>12</td>
<td>53%</td>
<td>58%</td>
</tr>
<tr>
<td>Category 2</td>
<td>Total</td>
<td>389</td>
<td>92%</td>
<td>72%</td>
<td>98</td>
<td>77%</td>
<td>54%</td>
</tr>
<tr>
<td>Category 3</td>
<td>146</td>
<td>32%</td>
<td>41%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* n: number of patients.

Abbreviations:

CDT : carbohydrate-deficient transferrin
GGT : gamma-glutamyl transpeptidase
Table III. – Specificity of CDT and GGT in patients in category 4 (weaned < 1 month) and category 5 (weaned > 1 month) according to age group.

Spécificité de la concentration sérique de la CDT et de l’activité sérique de la GGT chez les malades du statut 4 (sevrages inférieurs à 1 mois) et du statut 5 (sevrages supérieurs à 1 mois), en fonction de l’âge.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Category 4</th>
<th>Category 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n*</td>
<td>CDT</td>
</tr>
<tr>
<td>20-29</td>
<td>6</td>
<td>50%</td>
</tr>
<tr>
<td>30-39</td>
<td>18</td>
<td>72%</td>
</tr>
<tr>
<td>40-49</td>
<td>60</td>
<td>70%</td>
</tr>
<tr>
<td>50-59</td>
<td>17</td>
<td>65%</td>
</tr>
<tr>
<td>60-69</td>
<td>12</td>
<td>92%</td>
</tr>
<tr>
<td>Total</td>
<td>113</td>
<td>71%</td>
</tr>
</tbody>
</table>

* n: number of patients.

During the course of the study, 42 patients classified in category 1 (non-weaned) were later grouped into category 4 (weaned < 1 month). In these patients, serum CDT level declined significantly (111 ± 18 mg/L versus 57 ± 5 mg/L, P < 0.001) as did serum GGT (230 ± 85 IU/L versus 141 ± 74 IU/L, P < 0.001). In these patients, the specificity of serum CDT was 62% and the specificity of serum GGT was 19%. Results are presented by duration of weaning in table IV.

Fifty-three patients in category 4 (weaned < 1 month) were later classified in category 5 (weaned > 1 month). The serum CDT level in these patients declined significantly (56 ± 8 mg/L versus 41 ± 3 mg/L, P < 0.001) as did serum GGT (177 ± 66 IU/L versus 75 ± 26 IU/L, P < 0.01).

Forty-seven patients in category 5 (weaned > 1 month) were later classified in category 2 (relapse). The serum CDT level increased significantly in these patients (44 ± 3 mg/L versus 100 ± 17 mg/L, P < 0.01) as did serum GGT (62 ± 34 IU/L versus 176 ± 155 IU/L, P < 0.01).

Table IV. – Comparison of CDT and GGT in patients in category 1 (non-weaned) who were later classified in category 3 (weaned < 1 month) according to duration of weaning.

Comparaison des valeurs de la concentration sérique de la CDT et de l’activité sérique de la GGT chez 42 malades ayant le statut 1 (non sevrés) classés secondairement dans le statut 3 (sevrages inférieurs à 1 mois), en fonction du délai d’obtention du sevrage (Moyenne ± DS).

<table>
<thead>
<tr>
<th>Category</th>
<th>n*</th>
<th>CDT (mg/L)</th>
<th>CDT specificity</th>
<th>GGT (IU/L)</th>
<th>GGT specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1 (non-weaned)</td>
<td>42</td>
<td>111 ± 59</td>
<td>230 ± 269</td>
<td>164 ± 254b</td>
<td>13%</td>
</tr>
<tr>
<td>Category 3a (weaned 1-10 days)</td>
<td>16</td>
<td>67 ± 22</td>
<td>44%</td>
<td>164 ± 254b</td>
<td>13%</td>
</tr>
<tr>
<td>Category 3b (weaned 11-20 days)</td>
<td>16</td>
<td>55 ± 13a</td>
<td>56%</td>
<td>171 ± 271b</td>
<td>19%</td>
</tr>
<tr>
<td>Category 3c (weaned 21-30 days)</td>
<td>10</td>
<td>43 ± 8a</td>
<td>100%</td>
<td>54 ± 28b</td>
<td>30%</td>
</tr>
</tbody>
</table>

* n: number of patients; a P < 0.01 compared with value in category 1; b P < 0.05 compared with value in category 1.

Discussion

These findings demonstrate the good positive and negative predictive values of serum CDT for the evaluation of alcohol intake.

This work offers original data for comparing the diagnostic values of serum CDT and serum GGT in a large number of patients seen in an outpatient setting. Earlier studies on CDT have been generally conducted in inpatients (hospitals or weaning centers) [9-13]. Outpatient care centers offer supportive counseling, prevention, screening and care for alcohol-dependent or alcohol-abuse patients.

Studies evaluating serum CDT levels have used alcohol consumption levels varying from 40-80 g/d [11, 14-16]. The thresholds retained for this study (30 g/d for women and 50 g/d for men) were intermediate levels. Throughout the study, the patients’ level of alcohol consumption was determined with the face-to-face interview method. All estimations were performed by one physician highly experienced with this method. We did not use the DSM-III-R criteria [10], the DSM IV criteria [7, 14], or the CAGE or AUDIT questionnaires [17, 18]. With these questionnaires, a positive result orients towards alcohol abuse, without providing a quantitative estimation. Direct interview in a setting of confidence probably provides a better estimation [19].

In our study, the sensitivity of serum CDT level varied from 32% to 92% depending on the patient category. The sensitivity of CDT was better than that of GGT for patients in category 1 (92% versus 72%) and category 2 (77% versus 54%). In 1991, Stibler grouped the results of 21 studies conducted over 16 years in a total of 2500 patients with CDT results [5]. The sensitivity of CDT ranged from 52% to 100% depending on the study and assay method, with a mean of 82%. For patients with chronic liver disease with or without cirrhosis, the sensitivity was 35% in a group of 42 patients [11]. This diversity in sensitivity values is related to the heterogeneous nature of the study populations and severity of their liver disease, as well as the level of alcohol consumption, its duration, and the threshold level for serum CDT retained for the study. Conversely, we found that the sensitivity of serum CDT (41%) was better than that of CDT (32%) in patients in category 3 (moderate drinkers), especially in the subgroup of older subjects (50-59 years). Studies in the literature have reported GGT sensitivity ranging from 34% to 85%, depending on the severity of the liver disease, its association or not with other non-hepatobiliary disease, and patient age and gender [1]. In a study including 1202 patients, the sensitivity of serum CDT exhibited superior sensitivity over serum GGT in men aged less than 40 years [13].

In our study, the specificity of serum CDT varied from 71% to 96%, depending on the patient category. Specificity was however better than that of serum GGT (23%-62%). In the review of the literature performed by Stibler [5], specificity of CDT ranged from 80% to 100%, with a mean of 97%. False positives results were noted for certain genetic variants of transferrin (form D) or for carbohydrate-deficient glycoprotein syndrome, or more rarely for patients with primary biliary cirrhosis and chronic hepatitis C [5]. The specificity of GGT reported in the literature has been to the order of 50%, ranging from 11% to 85%. This level of specificity results from elevated GGT observed in patients with non-alcoholic liver disease, obesity, or dyslipidemia, or taking medications [1, 20].
Our findings confirmed the usefulness of serum CDT in following patients during the weaning process. We observed a significant decline in CDT levels in less than 11 days. The decline continued for up to one month of abstinence. The serum CDT level did not however return to normal in half of the patients. Consequently, a single assay is insufficient for early diagnosis of weaning and repeat tests must be performed. We also observed a significant decline in the serum GGT levels, but with less specificity.

Serum assay of GGT provides a specific and rapid assessment of abstinence [4]. In the event of relapse, we observed a significant increase in both markers. In the literature, serum CDT has been found to exhibit very good specificity (91.7%) in relapse patients as well as better responsiveness than serum GGT in terms of rapid increase [21]. Elevated CDT levels are observed as early as two weeks [22, 23]. During follow-up, intra-individual variations can identify periods of low-level resumed consumption [24, 25].

**Conclusion**

This study confirms the better diagnostic value of carbohydrate-deficient transferrin in comparison with gamma-glutamyl transpeptidase and suggests that carbohydrate-deficient transferrin could be used to follow outpatients, particularly to confirm weaning or screen for relapse.

**REFERENCES**