CARBOHYDRATE-DEFICIENT TRANSFERRIN: MARKER OF ACTUAL ALCOHOL CONSUMPTION OR CHRONIC ALCOHOL MISUSE?

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Abstract — Carbohydrate-deficient transferrin (CDT) is a useful indicator of excessive alcohol consumption with higher sensitivity and specificity than other markers that are used. In the present study, CDT was analysed in 161 patients hospitalized in a surgical ward to evaluate whether history of drinking and chronic alcohol misuse are important determinants of CDT elevations. Fifty-one of the patients were diagnosed as alcohol-dependent and they all reported a long history of alcohol abuse. Several of these, as well as many of the non-dependent patients, reported a high, recent alcohol consumption (>60 g/day for the previous 2 weeks). CDT performed better in detecting patients with alcohol dependency than in detecting patients with high alcohol consumption irrespective of dependency, showing higher sensitivity (47 vs 37%), likelihood ratio (4.7 vs 3.4), and a statistically significant difference in the receiver-operating characteristic curve areas \( (P = 0.04 \) in a two-tailed comparison test). In two subgroups, one with alcohol-dependent and one with non-dependent patients, consuming similar amounts of alcohol (range: 60–170 g/day), the sensitivity of CDT was 52 and 5%, respectively. We conclude that CDT is a better marker for patients with chronic alcohol misuse than as a marker for high actual alcohol consumption alone.

INTRODUCTION

Carbohydrate-deficient transferrin (CDT) is an ‘abnormal’ transferrin frequently used as a marker of excessive and chronic alcohol consumption. Stibler (1991), when introducing the test, suggested that serum CDT levels will increase after excessive drinking (more than 50–80 g per day) for a period of 2–3 weeks. However, frequency and intensity of alcohol consumption have also been suggested to influence CDT (Allen et al., 1994), and it is also known that the clinical utility of the CDT measurements is altered according to the population examined. Thus, the sensitivity of CDT in detecting alcohol abuse is lower among patients in general clinical settings than among patients admitted to detoxification treatments (Allen et al., 1994). Low sensitivities have been reported in general population studies (Nilssen et al., 1992; Gronbaek et al., 1995). In young, healthy subjects drinking voluntarily for a short time excessive amounts of alcohol, no or low-frequent increases in CDT were found (Salmela et al., 1994; Lesch et al., 1996). However, CDT is frequently and rapidly elevated in chronic alcoholics relapsing after a period of not drinking (Schmidt et al., 1997), indicating that alcohol-dependent subjects might be especially susceptible to effects from re-exposure to ethanol resulting in elevated CDT (Borg et al., 1994; Rosman et al., 1995).

Lesch et al. (1996) stated that CDT is a marker for chronic alcohol abuse with high sensitivity and specificity among alcohol-dependent subjects. They also reported that there was no correlation between blood-alcohol concentration and elevations of CDT. Niemelä et al. (1995) described higher CDT levels in early phases of alcoholic liver diseases and Yamauchi et al. (1993) concluded that CDT is a useful marker of non-cirrhotic alcoholic liver diseases. These studies suggest that other features beyond alcohol consumption alone, such as long-term alcohol abuse and chronicity of the alcohol problem have effects on CDT levels, as recently reported by Saini et al. (1997).

In two previous reports, we have evaluated CDT
in hospitalized patients including abstainers, low and high consumers and alcohol-dependent patients. We found that CDT is frequently elevated among middle-aged, alcohol-dependent male patients (Huseby et al., 1997a,b) and that the sensitivity of CDT increases with higher consumption. In the present study, we have reanalysed the patients and compared the diagnostic performance of CDT as a marker of chronic alcohol misuse to that of actual alcohol consumption. The comparison was performed after dividing the patients either into alcohol-dependent (who all reported a long history of alcohol abuse) or non-dependent, or into recent high consumers (≥60 g/day) or low consumers (<60 g/day) irrespective of dependency.

**PATIENTS AND METHODS**

*Patients*

The patients were hospitalized in a surgical department at the University Hospital of Lübeck and have been described in detail in our previous studies (Huseby et al., 1997a,b). In the present study, we excluded those patients who had not reported (or did not want to report) their recent alcohol consumption (meaning daily consumption over the previous 2 weeks), and those patients from whose serum samples we now lacked sufficient amounts for renewed %CDT analysis. The patients consisted of 161 otherwise unselected subjects admitted to an acute surgical ward. Among these, 51 were diagnosed as alcohol-dependent according to SCAN interviews (WHO, 1992a) (section 11: Abuse) complying with both ICD-10 (WHO 1992b) and DSM-III-R (American Psychiatric Association, 1987) criteria. The remaining 110 patients did not meet these criteria and were classified as non-dependent. The patients were also interviewed at admittance about their alcohol consumption for the previous 2 weeks (DOSE: mean consumed g of pure alcohol/day). The alcohol-dependent patients had >10-year history of drinking and had had at least one detoxification treatment period. All non-dependent patients, including the high consumers, had <10-year history of drinking and had not been subject to detoxification. The alcohol consumption for the whole patient group ranged between 0–800 g/day, median value: 36 g/day. The alcohol consumption for the alcohol-dependent patients ranged between 0–800 g/day with a median DOSE value of 63 g/day. Among the non-dependent patients, the alcohol consumption ranged between 0–162 g/day, median DOSE was 26 g/day. Most patients in this group (91 of the 110) consumed quantities of ethanol of <60 g/day. The remaining 19 non-dependent patients reported a higher consumption (60–162 g alcohol/day), with mean and median values of 92 and 78 g/day, respectively. A comparable group (n = 21) was selected from among the alcohol-dependent patients (consuming ≥60 g/day but less than 170 g/day); their alcohol intake mean and median values were 92 and 84 g/day, respectively. The alcohol-dependent patients from the surgical ward had a median age of 45.0 years, and the non-dependent patients had a median age of 43.5 years. All patients voluntarily joined the programme, which complied with the Helsinki declaration of 1975.

*Blood sampling and analysis*

A venous blood sample was drawn from the patients at inclusion and serum was kept frozen at −70°C until analysed. CDT measurement was performed by the AXIS %CDT Turbidimetric Immunoassay (TIA) kit from AXIS Biochemicals ASA (Oslo, Norway). This kit separates the transferrin isoforms by micro columns and quantifies CDT by turbidimetry. The analytical procedure was performed as described by the manufacturer. The cut-off value was selected as 6% according to the manufacturer’s instructions. The coefficient of variation (CV) values were 4.3% between days for a control serum accompanying the kit. Serum samples had been stored (at −70°C) for 2.5 years, which, according to the manufacturer, should not influence the %CDT TIA levels.

*Data analysis and software*

Statistical analyses were performed using the StatGraphics Plus for Windows program (Manugistics, Rockville, MD, USA). Receiver-operating characteristic (ROC) curves and areas under these curves were estimated by the GraphROC for Windows program (V. Kairisto, University of Turku, Finland) (Kairisto and Poola, 1995). Sensitivity, specificity, and likelihood ratios were calculated by using this program, which also calculated P-values for two-tailed test for significance of differences after unpaired comparison of
Table 1. Diagnostic performance of carbohydrate-deficient transferrin as a marker of chronic alcohol misuse or as a marker of actual alcohol consumption

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Sensitivity (%)</th>
<th>Likelihood ratio</th>
<th>ROC curve area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol-dependent (n = 51)</td>
<td>47</td>
<td>4.7</td>
<td>0.78</td>
</tr>
<tr>
<td>Alcohol consumers (n = 49)</td>
<td>37</td>
<td>3.4</td>
<td>0.65*</td>
</tr>
</tbody>
</table>

*P = 0.04 from a two-tailed test of significance in the difference of receiver-operating characteristic (ROC) curve areas. Mean and median values of alcohol intake are given in Patients and methods. Sensitivity and likelihood ratio were calculated at specificity selected as 90%.

areas under the ROC curves. Figures were compiled using the Fig.P for Windows program (BioSoft, Cambridge, UK).

RESULTS

Among the 51 alcohol-dependent patients, 47% (24/51) showed elevated CDT. When dividing all the 161 patients according to recent alcohol consumption, 49 patients reported a consumption of 60 g/day or higher, and 39% of these (19/49) showed elevated CDT. As shown in Table 1 and Fig. 1, significantly higher sensitivities, likelihood ratio values (calculated at a specificity of 90%), and ROC curve areas, were found when CDT was used as a marker of chronic alcohol misuse compared to CDT as a marker of alcohol consumption (DOSE).

A weak, but significant, correlation was found between DOSE and CDT for all patients (P = 0.0004, n = 161, correlation coefficient = 0.28). However, a more diverse pattern was seen when studying subgroups of the patients. The correlation between DOSE and CDT was significant for the 51 alcohol-dependent patients (P = 0.006, n = 51, correlation coefficient = 0.39), but not significant for all the non-dependent patients (P = 0.99, n = 110) or the non-dependent patients consuming 60 g/day or more (P = 0.30, n = 19, correlation coefficient = -0.24). When selecting the alcohol-dependent patients consuming more than 90 g alcohol/day, no significant correlation was found (P > 0.05) between CDT and DOSE.

The highest alcohol intake reported among the non-dependent patients was 162 g/day. A group of 19 non-dependent patients reported a consumption of 60–162 g/day, but only one of these patients (5%) showed elevated CDT. A comparable group for alcohol intake was selected among the alcohol-dependent patients; 21 of these reported consumption of 60–170 g/day (mean: 92 g/day; median: 84 g/day) and 52% of these (11/21) showed CDT ≥6%. The individual CDT values of these 21 alcohol-dependent, and of the 19 non-dependent, subjects are plotted in Fig. 2.

DISCUSSION

Several investigators have documented that CDT shows high sensitivity and specificity in populations with heavy consumption of alcohol, and have suggested that CDT is a useful marker in detecting patients with alcohol intake >60 g/day over a prolonged period of time. Recent studies have shown that CDT is also influenced by age, sex, and particularly by history of drinking (Yamauchi et al., 1993; Niemelä et al., 1995; Yersin et al., 1995; Huseby et al., 1997a; Saini et al., 1997).

In the present study we found a significantly
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Fig. 2. Carbohydrate-deficient transferrin (CDT) values in heavy drinking alcohol-dependent and non-dependent subjects.

CDT values were measured in 21 alcohol-dependent (A) and 19 non-dependent (B) subjects reporting a recent alcohol intake of 60-170 g/day.

Better performance for CDT in diagnosing the alcohol-dependent patients, than in detecting those with an actual high consumption. The alcohol-dependency syndrome is mainly defined as a behavioural pattern. A central descriptive characteristic of the dependence syndrome is the desire or the concept of craving which cannot be measured by a marker of consumption. However, the alcohol-dependent patients in the present study were reported to have a longer and more severe history of alcohol abuse (self-report) than the non-dependent patients, including those with recent high alcohol consumption. We could therefore focus on whether long-term abuse resulting in alcohol dependency will be a stronger determinant of CDT changes than actual alcohol intake alone. This finding was substantiated when selecting patients consuming 60-170 g/day; 19 non-dependent and 21 alcohol-dependent patients reported a recent alcohol intake in this range. Only one of the 19 non-dependent patients (5%) had an elevated CDT value, compared with 11 of the 21 alcohol-dependent patients (52%). A further support for the findings came from the lack of correlation that was found between CDT and DOSE among the non-dependent patients and also among the alcohol-dependent patients consuming high amounts of alcohol.

In our previous report, we also described a group of patients from a detoxification ward, diagnosed as alcohol-dependent (Huseby et al., 1997a). These patients reported very high consumption of alcohol (0-920 g/day, median value: 240 g/day). We reanalysed available serum samples from patients with reported alcohol intake and found that this group had a much higher sensitivity for CDT than the patients analysed in the present study (data not shown). This could only be a result of a long history of very high alcohol consumption in these detoxified patients, and further confirm that alcohol misuse must be heavy and on-going over a long period of time before CDT is significantly elevated.

Several reports have indicated that CDT is not a good parameter of alcohol misuse in women (Allen et al., 1994; Gronbaek et al., 1995; Huseby et al., 1997a). In our previous study (Huseby et al., 1997a), we did not find any significant difference in alcohol consumption between men and women, but observed lower specificity of CDT for women. In the present study, we calculated the sensitivities for men only by excluding females, but no significant changes in CDT were detected.

Lesch et al. (1996) did not find significant elevations among young subjects voluntarily drinking excessive amounts of alcohol. They indicated that CDT is a chronic alcohol misuse marker for patients reaching the early phases of alcoholic liver disease. A similar conclusion has been reached by others (Bell et al., 1994; Niemelä et al., 1995; Saini et al., 1997).

Our data support these studies and we conclude that chronic alcohol misuse is a strong determinant of CDT elevation, and that CDT is a good marker of patients with long-term alcohol problems. A major issue may therefore be whether CDT elevation coincides with the early stages of alcoholic liver diseases, and further investigations of the regulation of transferrin biosynthesis and glycosylation are clearly needed.

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REFERENCES


WHO (1992a) Schedules for Clinical Assessment in Neuropsychiatry. WHO Division of Mental Health, Geneva.

