MEASUREMENT OF CARBOHYDRATE-DEFICIENT TRANSFERRIN (CDT) IN A GENERAL MEDICAL CLINIC: IS THIS TEST USEFUL IN ASSESSING ALCOHOL CONSUMPTION?

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Abstract — The aim of this study was to measure serum carbohydrate-deficient transferrin (CDT) in consecutive patients attending a general medical clinic with a range of alcohol intakes to determine its value in assessing such intake. Eighty-one consecutive patients (42 male, 39 female) aged 20-85 years (median = 49.5 years) attending an out-patient clinic were selected for the study. Each patient completed an alcohol diary detailing the units of alcohol consumed in the previous week, a CAGE questionnaire and an alcohol history, and underwent conventional blood tests including mean corpuscular volume (MCV), liver function tests, and γ-glutamyl transferase (GGT). CDT was estimated using an enzyme immunoassay (CDTect, Pharmacia). The group comprised of 17 teetotallers, 28 light (<100 g/week), 23 moderate (100-400 g/week), and 13 heavy (>400 g/week) drinkers. Median serum CDT for heavy drinkers (25.5 U/l) was significantly higher than for the rest (median = 17 U/l, Kruskal–Wallis test, \( P = 0.01 \)). Serum CDT correlated significantly with the CAGE score (Mann–Whitney test, \( P = 0.01 \)), but poorly with alcohol diary records (\( r = 0.1, P = 0.4 \)). However the correlations between GGT and diary records (\( r = 0.43, P = 0.001 \)) and MCV with diary records (\( r = 0.5, P < 0.001 \)) were significant. Sensitivity, specificity, and positive predictive value for elevated serum CDT were 69, 81 and 41% respectively in detecting heavy drinking. The positive predictive values for the various parameters were 43% for elevated serum GGT, 41% for raised erythrocyte MCV, and 75% for a positive score on the CAGE questionnaire. When a combination of the markers CDT, GGT, and MCV was used, elevation in two of the three markers detected heavy drinking with sensitivity of 85%, specificity of 88%, and positive predictive value of 61%. We conclude that, in out-patients with a wide range of alcohol intakes conventional markers such as serum GGT and erythrocyte MCV were more suitable than serum CDT for assessing alcohol intake. Serum CDT when used in combination with serum GGT and erythrocyte MCV was useful in detecting heavy drinking. The importance of careful history-taking including a standardized questionnaire is emphasized.

INTRODUCTION

Carbohydrate-deficient transferrin (CDT) is a collective term referring to the isoforms of transferrin which are deficient in sialic acid residues. The reason for the alcohol-induced increase in serum CDT is not established. The accumulation of CDT has been attributed to acetaldehyde-mediated inhibition of post-translational protein glycosylation (Stibler and Borg, 1991), increased desialylation of completely glycosylated transferrin molecule (Lof et al., 1996), and impaired hepatic binding of asialoglycoproteins (Casey et al., 1991). Serum CDT measurement has been widely examined as a marker of excessive alcohol consumption. The sensitivities and specificities of this test have ranged in different patient populations from 22% (Nystrom et al., 1992) to 91% (Stibler et al., 1978), and 80% (Rosman et al., 1995) to 100% (Niemela et al., 1995) respectively. The reference range for serum CDT is different for women and the test performs less well in females (Nystrom et al., 1992), probably due to varying levels of circulating asialo- and monosialo-transferrin (Sillanaukee, 1996). Serum CDT has low sensitivity in detecting heavy drinking in those under the age of 30 years (Bisson and Milford-Ward, 1994).

This marker has often been judged by comparing values in patients who are clearly alcohol-dependent and with abstainers or very light...
drinkers. We have therefore examined serum CDT in out-patients attending a general medical clinic with a wide range of alcohol intakes in order to determine fully its value in assessing alcohol consumption in a non-selected population. Screening patients in a medical clinic for excess alcohol consumption using a reliable biochemical marker would clearly be important, because of the potential for detecting occult alcohol abuse as an explanation for a clinical problem.

PATIENTS AND METHODS

Eighty-one individuals (43 male, 38 female) aged 20–85 years (median = 49 years) attending an out-patient medical clinic were randomly selected for the study. Each patient completed an alcohol diary detailing the amount and type of alcoholic drink consumed on each day during the week before with confirmation from patient's attendant (partner, close relative or friend). Each patient completed a CAGE questionnaire (Beresford et al., 1990). An aggregate score of 2 or more (out of a maximum of 4) was considered CAGE-positive (Yersin et al., 1995).

Patients were grouped as teetotallers (n = 17), light (<100 g/week, n = 28), moderate (100–400 g/week, n = 23), and heavy drinkers (>400 g/week, n = 13). Each individual underwent conventional liver function tests (LFT) including estimation of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, and γ-glutamyl transferase (GGT). All biochemical assays listed were performed using spectrophotometric analysis on a Hitachi 717 routine clinical chemistry analyser (Boehringer Mannheim) at 37°C. Erythrocyte mean corpuscular volume (MCV) was determined using an automated Coulter counter analyser STKS-2. CDT was estimated using enzyme immunoassay (CDTect, Pharmacia) with colorimetric endpoint.

A mean value ± 2 SD in the healthy population was chosen as a 'cut-off' value for each laboratory test which was 96 fl for MCV, 45 U/l for GGT, 40 U/l for AST and ALT, 90 U/l for ALP, and 17 μmol/l for bilirubin. 'Cut-off' values for CDT were 21 U/l for men and 26 U/l for women as recommended by the manufacturers.

Statistical analysis

Many of the variables, including CDT, were positively skewed and were therefore logged for the purposes of statistical analysis. The correlation

Fig. 1. Serum carbohydrate-deficient transferrin (CDT) levels in the study population. Values are shown for the subgroup of heavy drinkers (median 25.5 U/l) and for the rest of the study group (median 17 U/l).
between serum CDT levels and other continuous variables was assessed using Spearman's rank correlation coefficient. Log of CDT was compared between groups using the Mann–Whitney (two groups) and Kruskal–Wallis (more than two groups) tests of equality of populations. Standard methods were used for assessing sensitivity, specificity, and positive predictive value using the 'cut-off' levels established.

RESULTS

Median serum CDT levels were significantly higher in heavy drinkers \( n = 13, \) median \( = 25; \) range \( 11–66 \ U/l \) when compared with the rest of the patients \( n = 68, \) median \( = 17; \) range \( 5–38 \ U/l, \) Kruskal–Wallis test, \( P = 0.01, \) Fig. 1). Median CDT levels were higher in male heavy drinkers \( n = 10, \) median \( = 25.5; \) range \( 16–66 \ U/l \) when compared with the rest of the male patients studied \( n = 33, \) median \( = 14.5; \) range \( 5–34 \ U/l, P = 0.004. \) There was no significant difference among female patients between heavy drinkers \( n = 3, \) median \( = 20; \) range \( 11–34 \ U/l \) and the rest \( n = 35, \) median \( = 18.5; \) range \( 6–38 \ U/l, P = 0.4. \)

Median serum CDT levels were significantly higher in CAGE-positive patients \( \text{CAGE} \) score \( = 2 \) or more, \( n = 11, \) median \( = 25; \) range \( 11–38 \ U/l \) when compared with CAGE-negative individuals \( \text{CAGE} \) score \( = 0 \) or \( 1, \) median \( = 17; \) range \( 5–66 \ U/l, \) Mann–Whitney test, \( P = 0.01, \) Fig. 2), but again considerable overlap in the results is evident (Fig. 2). There was poor correlation between serum CDT levels and alcohol consumption \( (U/week) \) as per diary records (Fig. 3) (Spearman's rank correlation coefficient, \( r = 0.1, P = 0.4. \) There was a significant correlation between serum GGT and diary records \( (r = 0.43, P = 0.001) \) and better correlation between erythrocyte MCV and diary records \( (r = 0.5, P < 0.001). \) There was no relationship between serum CDT and other conventional LFTs.

Performances of various parameters in detecting heavy drinking are shown in Table 1. Elevated serum CDT levels detected nine of 13 heavy drinkers with a sensitivity of 69% and specificity of 80.9% \( (55/68), \) and a positive predictive value of 40.9% \( (9/22). \) Serum CDT had a sensitivity of 80% \( (8/10), \) specificity of 72% \( (23/32), \) and positive predictive value of 47% \( (8/17) \) among male patients while in females these values were 33% \( (1/3), \) 88% \( (32/36), \) and 20% \( (1/5) \) respectively. Elevated serum GGT identified 10 out of 13 heavy drinkers with sensitivity of 77% and a specificity of 81% \( (55/68) \) and a positive predictive value of 43% \( (10/23). \) Raised erythrocyte MCV had a sensitivity of 54% \( (7 \) of 13 heavy
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Fig. 3. Correlation between serum carbohydrate-deficient transferrin (CDT) and alcohol consumption levels.

drinkers) and specificity of 85% (58/68) and positive predictive value of 41% (7/17). CAGE positivity (score of 2 or more) had a sensitivity of 69% ($n = 9/13$) and a specificity of 95% (65/68) in identifying heavy drinkers with a positive predictive value of 75% (9/12). When elevations of any two of the three markers (CDT, GGT, and MCV) were used to detect heavy drinking, a sensitivity of 85% (11/13), a specificity of 88% (65/68) and a positive predictive value of 61% (9/12) were obtained.

**DISCUSSION**

The biological, clinical, and social effects of alcohol abuse have long made evident the need for a reliable biochemical marker to identify consumers at risk. Serum CDT has a half-life of about 2 weeks (Gjerde et al., 1988) and so will reflect chronic alcohol abuse within the recent past. However, there are issues to be resolved. Firstly previous studies have included highly selected groups (Nystrom et al., 1992; Bisson and Milford-Ward, 1994) or have compared serum CDT values in patients who already have alcohol-related symptoms with abstainers or very light drinkers (Rosman et al., 1995; Niemela et al., 1995). These are highly artificial situations (Conigrave et al., 1995). Reports of sensitivity and specificity from such studies have also varied widely. In contrast, we have studied an unselected patient group from a realistic setting of a general medical clinic in whom detection of occult alcohol abuse is of clinical relevance. Our results do not support the use of serum CDT as a marker in this setting. The nature of the drinking pattern, including quantity and frequency necessary to raise levels of serum CDT significantly remains unclear (Allen et al.,

Table 1. Performances of various parameters in detecting heavy alcohol drinking

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity % ($n$)</th>
<th>Specificity % ($n$)</th>
<th>Positive predictive value % ($n$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDT</td>
<td>69 (9/13)</td>
<td>81 (55/68)</td>
<td>41 (9/22)</td>
</tr>
<tr>
<td>GGT</td>
<td>77 (10/13)</td>
<td>81 (55/68)</td>
<td>43 (10/23)</td>
</tr>
<tr>
<td>MCV</td>
<td>54 (7/13)</td>
<td>85 (58/68)</td>
<td>41 (7/17)</td>
</tr>
<tr>
<td>Abnormalities in two of the three tests</td>
<td>85 (11/13)</td>
<td>88 (61/88)</td>
<td>61 (11/18)</td>
</tr>
<tr>
<td>CAGE score</td>
<td>69 (9/13)</td>
<td>95 (65/98)</td>
<td>75 (9/12)</td>
</tr>
</tbody>
</table>

CDT = carbohydrate-deficient transferrin; GGT = $\gamma$-glutamyltransferase; MCV = mean corpuscular volume.
1994). Even with a consumption of more than 60 g/day, studies have found a slight or no correlation between amount consumed or blood-alcohol levels and serum CDT value (Stibler et al., 1986; Kwoh-Gain et al., 1990), suggesting that CDT may depend only indirectly on ethanol. The predictive value of serum CDT for drinking in the range of 30–50 g/day has been shown to be low (Gronbaek et al., 1995). Our findings of a poor correlation of serum CDT levels with a wide range of alcohol consumption raise doubts about its clinical applications. In a general medical clinic, where a lower range of drinking may have an impact on individual clinical problems, measurements of serum CDT appear to have a limited role. In an out-patient clinic, measurements of MCV and GGT are readily available, show better correlation with alcohol diary records, and are more suitable for routine use. Overall, the performance of serum CDT was disappointing for the detection of excess alcohol intake in our population with a positive predictive value of 40% which was similar to serum GGT (43%) and erythrocyte MCV (41%). The CAGE questionnaire was more useful with a positive predictive value of 75%. Another study involving patients in an emergency admission unit showed blood MCV and GGT to be comparable to serum CDT in screening for excessive drinking (Yersin et al., 1995). The poor performance of serum CDT in women highlighted by previous studies (Nystrom et al., 1992) has been emphasized by our findings. This further limits the use of the test in a general medical clinic. In our study, only six of the 81 subjects were aged under 30 years and we are unable to comment on the usefulness or otherwise of CDT measurement in patients under the age of 30 years.

We have shown that serum CDT levels were significantly higher in heavy drinkers and alcohol-dependent (CAGE positive) subjects, when compared with the rest of the study group. Serum CDT can be used to complement other markers such as serum GGT and erythrocyte MCV with increased sensitivity and specificity when used in combination. In the present study, the positive predictive value of serum CDT alone of 40% was increased to 61% when using the elevation of any two markers (CDT, GGT or MCV) to identify heavy drinking. Hence combination of tests is a more useful aid in detection of excessive alcohol consumption.

In subjects with underlying alcoholic liver disease, elevated serum GGT and erythrocyte MCV may not resolve even with abstinence (Rosalki, 1984) and cannot be used to monitor drinking behaviours. Increasing the sensitivity of serum CDT by introducing individualized cut-off values between normal and elevated CDT levels has been shown (Borg et al., 1995; Helander et al., 1996) to be helpful in long-term monitoring of alcohol-dependent patients. Hence, serial CDT estimation may have a potential role in monitoring abstinence in patients with alcoholic liver disease.

We conclude that CDT is of limited value for screening in a general medical clinic where a broad range of alcohol intake is represented. The test may be of value in detecting heavy drinking when used in combination with MCV and GGT.

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