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Carbohydrate-deficient transferrin is not a useful marker for the detection of chronic alcohol abuse

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Abstract

Background The role of carbohydrate-deficient transferrin (CDT) as a reliable marker for the detection of chronic alcohol abuse has been discussed controversially.

Methods Therefore, we investigated CDT in the sera from 405 subjects with different alcohol intake. Besides healthy control subjects ($n = 42$), inpatients and outpatients in a department of gastroenterology ($n = 325$) and patients admitted to a department of otorhinolaryngology ($n = 38$) were studied. A total of 213 patients suffered from various forms of liver diseases, and 89 patients had liver transplantation. CDT values were determined by a double-antibody radioimmunoassay.

Results In the 241 alcohol-abstinent subjects, CDT levels ranged from 3 to 90 units L^{-1} (median = 12); the 92 moderate drinkers (20–60 g of alcohol per day) showed values from 3 to 40 units L^{-1} (median = 12), and the 72 subjects with chronic alcohol abuse (> 60 g per day) revealed CDT levels from 3 to 100 units L^{-1} (median = 16). The diagnostic specificity for alcohol abuse was 86·8% for men (sensitivity 36·9%) and 95% for women (sensitivity 0%).

Conclusion Our data indicate that measurement of CDT does not reach clinical use in the detection of chronic alcohol abuse in an unselected population because of its insufficient specificity and sensitivity.

Keywords Alcohol abuse, alcohol marker, carbohydrate-deficient transferrin.
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Introduction

During the last years, there have been many attempts to develop a parameter for the detection of chronic alcohol abuse. One of the first studies was made on cerebrospinal fluids from patients with alcoholic cerebellar degeneration and revealed an atypical form of transferrin, a desialylated isoform [1]. Later, this protein, called carbohydrate-deficient transferrin (CDT) was isolated from sera from such patients [1]. The mechanism responsible for the formation of this abnormal transferrin molecule is not clear. It may be caused by inhibition of the glycosyl transfer mediated by acetaldehyde [1,2]. Using isoelectric focusing – the reference method for the detection of CDT [3–5], Stibler *et al*. [6] developed an assay that consists of an anion exchange chromatography followed by radioimmunoassay. This test is now commercially available in a modified version [6,7]. For this method Stibler *et al*. [1] reported a specificity of 99% and a sensitivity of 93% for the identification of chronic alcohol abuse, defined as regular intake of ≥ 60g of ethanol per day. Thereafter, other reports confirmed the high specificity, although the sensitivity in these studies ranged from very low (22%) to very high (> 80%) [3,5,8–13]. With the exception of primary biliary cirrhosis, severe hepatic failure, carbohydrate–deficient glycoprotein syndrome and pregnancy [1,14–16], CDT measurement is now widely recommended as a means to discriminate between persons with and those without chronic alcohol intake [11,14,17,18]. Because of serious personal and possibly clinical consequences of the outcome of such a test, we evaluated the clinical use of the CDT test in a well-defined, although

Abbreviations: CDT, carbohydrate deficient transferrin; γ-GT, γ-glutamyltransferase; MCV, mean corpuscular volume.

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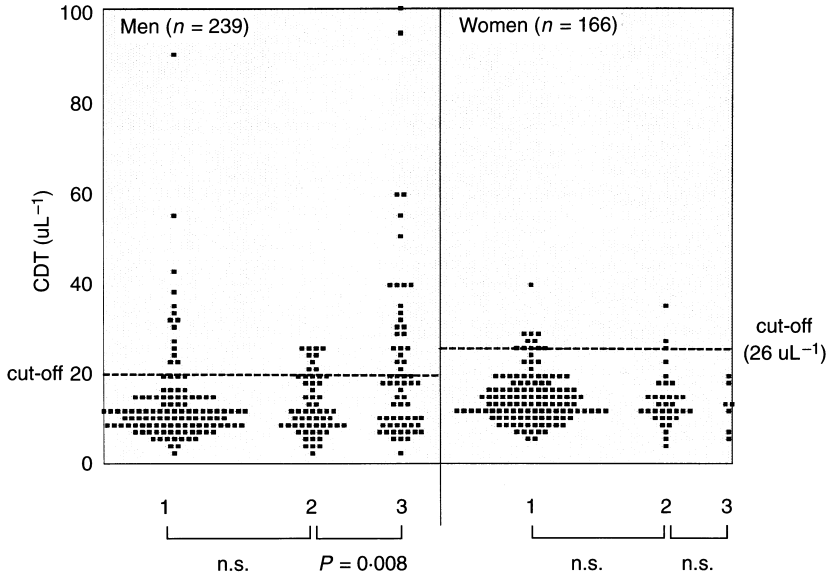

Figure 1 Distribution of carbohydrate-deficient transferrin (CDT) values for the whole patient group ($n = 405$). 1, Abstinent; 2, moderate drinkers (20–60 g per day); 3, alcohol abusers ($\geq$ 60 g per day). n.s., not significant.

unselected, group of subjects focusing on the following points:

1 whether a low CDT value can exclude chronic alcohol abuse;
2 whether a high CDT value is a reliable marker for alcohol intake;
3 whether the CDT test is helpful in differential diagnosis of patients with abnormal γ-GT or MCV test results of unknown origin; and
4 whether measurement of CDT is relevant for the control of abstinence in a patient.

Patients and methods

Patients

The study was performed as a blind prospective trial on sera from 405 persons (239 men, 166 women). Fourteen were patients admitted to the Department of Internal Medicine, Hospital München-Schwabing, 54 were admitted to the second Department of Medicine Klinikum Grosshadern Munich and 257 were outpatients at the same department; 38 patients were admitted to the Department of Otorhinolaryngology at the Klinikum Grosshadern, Munich.

A total of 89 patients underwent liver transplantation, 213 patients suffered from various liver diseases (31 alcohol-related hepatopathias including fatty livers, 36 hepatopathias of unknown origin, five alcohol-related liver cirrhoses, 29 cirrhoses of other origin, 89 chronic hepatitis B and C, four autoimmune hepatitis and five primary biliary cirrhoses, 14 from various liver diseases, such as liver cell carcinoma, liver metastases, benign liver tumours, haemochromatosis, cholecystitis with and without lithiasis) and 36 patients had different internal diseases without liver dysfunction. Diagnosis was based on the general clinical status and follow-up of the subjects, on biopsies in liver cirrhosis and haemochromatosis, on serology in hepatitis B and C, immunological laboratory tests in autoimmune hepatitis (antimitochondrial and antinuclear antibodies), on sonography in fatty livers and cholecystolithiasis. One liver cell carcinoma was biopsy-proven, whereas the others were diagnosed by increased alphafetoprotein and ultrasound.

The 14 patients admitted to the hospital München-Schwabing came for alcohol withdrawal and were observed during a follow-up investigation over a period of 14–39 days.

A total of 333 subjects from the whole-patient group had an alcohol consumption < 60 g per day and 72 had a chronic alcohol intake $\geq$ 60 g per day. A total of 42 subjects (18 men, 24 women) served as healthy control subjects.

Alcohol history

Alcohol history and intake was accurately explored by careful patient interviews. For every department, it was always the doctor responsible for the study who asked the patients about their daily alcohol consumption, using the same procedure in all institutions. In the questionnaire the patients were asked about their drinking habits, the kind of alcohol consumed and the quantity, in glasses or bottles. The quantities were calculated in grams of alcohol per day. Chronic alcohol abuse was defined as a daily alcohol intake $\geq$ 60 g per day for more than 2 weeks. For this study, regular daily alcohol consumption was relevant for classification, but episodic excessive drinking was not.

Laboratory tests

In addition to CDT, γ-glutamyltransferase (γ-GT) and mean corpuscular volume (MCV), two of the common

Table 1 Distribution of CDT values, according to different alcohol consumption, sex and CDT ranges.

			< g Alcohol per day					> 60 g Alcohol per day				
		n	units L^{-1}: 0–10	11–20	21–30	31–50	51–100	0–10	11–20	21–30	31–50	50–100
Abstinent	M	116	58	44	7	5	2					
	F	125	29	80	15	1						
Moderate drinkers	M	58	29	20	9							
	F	34	9	21	3	1						
Alcohol abuse	M	65						25	16	13	7	4
	F	7						2	5			
Head and neck cancer	M	38						18	9	5	2	4
Healthy control subjects	M	18	8	6	2			1	1			
	F	24	11	11	2							
Mixed internal diseases	M	15	9	1					1	1	3	3
	F	20	8	8	1			1	2			
Alcoholic hepatopathies	M	29						12	5	8	2	2
	F	2							2			
Hepatopathies of unknown origin	M	17	10	6		1			3	1	1	
	F	19	7	9	3				1			
Alcoholic cirrhosis	M	4							2	2		
	F	1							1			
Cirrhosis of other origin	M	17	3	5	7	2						
	F	12		7	5							
Chronic hepatitis B, C	M	55	25	23	4	1	1		1			
	F	34	4	28	2							
Autoimmune hepatitis and PBC	M	2	1	1								
	F	7	3	4								
Other liver diseases	M	10	5	4	1			1				
	F	4	2	2								
Liver transplantation	M	48	17	25	2	2	1			1		
	F	41	8	26	4	1						

Table 2 Clinical use of carbohydrate-deficient transferrin (CDT) calculated by the chi-square test. The significant *P*-value depends on the large number of persons with a low daily alcohol consumption.

	Alcohol abuse	
	+	−
CDT		
+	26	54
−	46	279

$P = 0{\cdot}001$.

parameters for the control of excessive alcohol consumption, were determined in all patients. In the follow-up investigation, alcohol abstinence was confirmed by measuring the blood alcohol concentration (BAC) using the alcohol oxygenase method (bioMèrieux sa, Marcy l'Etoile, France). γ-GT was measured, using the method of Szach (25 °C, pH 8·25), on the Hitachi 747 (Boehringer Mannheim, Germany), and MCV was measured using the impedance method (Coulter STKS, Miami, USA). All clinical chemical measurements were performed in the Institute of Clinical Chemistry, Klinikum Grosshadern, Munich with the exception of BAC, which was measured in the Institute of Clinical Chemistry, Städtisches Krankenhaus München-Schwabing. All samples measured in the Institute of Clinical Chemistry were blinded for the laboratory.

CDT measurement

The blood was taken on the first morning of hospitalization, for outpatients on the morning of their presentation to the department of gastroenterology. After centrifugation sera were stored at −70 °C until analysis using a double-antibody radioimmunoassay (Kabi Pharmacia, Uppsala, Sweden). The principle of this assay consists of two steps: first the separation of transferrin into different isoforms, using a microcolumn technique. CDT in the eluate competes with a fixed amount of ^{125}I-labelled transferrin for the specific antibodies. Free and bound transferrin are separated by the addition of a second antibody immunoadsorbent, followed by centrifugation and decanting. The radioactivity measured is inversely proportional to the quantity of CDT in the sample.

Statistical analysis

Data are given as median and ranges. Differences between groups were evaluated using Wilcoxon's test for paired data and two-sample rank-sum test for unpaired data. A *P*-value of less than 0·05 was considered to be significant.

Analogue results were obtained on subjecting the data to the Student's *t*-test.

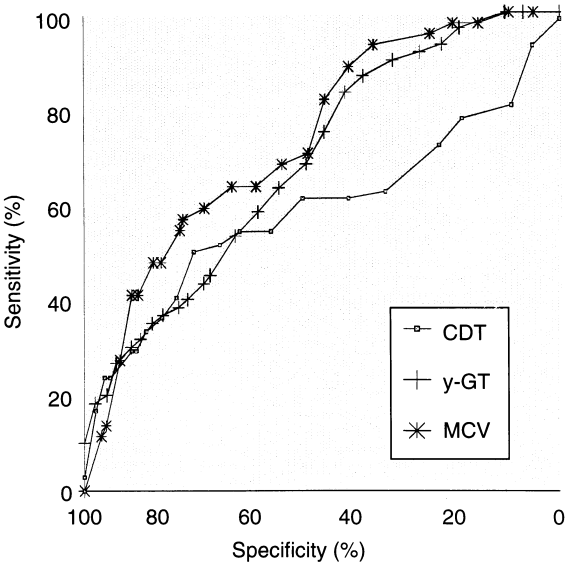

Figure 2 Receiver-operating characteristic (ROC) analysis of subjects with daily alcohol intake ≥60 g per day ($n = 72$) vs. those with alcohol consumption < 60 g per day for carbohydrate-deficient transferrin (CDT), γ-glutamyltransferase (γ-GT) and mean corpuscular volume (MCV). The closer this curve comes to the upper left corner of the square (100% sensitivity with 100% specificity), the greater is the power of discrimination between the group of drinkers and the reference group.

The calculation of clinical use was performed using the chi-square test.

Results

Intra- and interassay variance for CDT

The within-run imprecision of the test was 13% ($\bar{x} = 32$ units L^{-1}, 10 replicates of the same serum sample). The between-run imprecision was 12% determined in five runs on duplicates of a serum pool ($\bar{x} = 15$ units L^{-1}).

Distribution of values

The total range of CDT concentration was 3–100 units L^{-1}. The highest CDT value (100 units L^{-1}) was obtained in a patient with a pharyngeous carcinoma and a daily alcohol intake of 250 g. In the group of abstinent subjects, the highest CDT value was 90 units L^{-1} in a 62-year-old male patient after liver transplantation but without signs of liver or other dysfunction. In female patients there were no significant differences between the distribution of CDT values in the abstinent group (5–40 units L^{-1}), patients with a moderate daily alcohol intake (4–36 units L^{-1}) and those with chronic alcohol abuse (5–20 units L^{-1}) (Fig. 1). In contrast, male patients showed a significant difference ($P = 0{\cdot}008$) between

Table 3 Characteristics of patients with liver diseases and distribution of carbohydrate-deficient transferrin (CDT) and γ-glutamyltransferase (γ-GT) values.

				CDT units L^{-1}			
	n	Age range (median)	Male/female	Range	5% percentile	Median	95% percentile	γ-GT range (median)
Alcoholic hepatopathies	31	30–77 (47)	29/2	5–95	7	13	39	8–1000 (73)
Hepatopathies of unknown origin	36	29–81 (59)	17/19	4·8–25	6	11	21	6–316 (37)
Alcoholic cirrhosis	5	44–65 (49)	4/1	13–33		19		30–448 (51)
Cirrhosis of other origin	29	29–73 (41)	17/12	7–42	8	20	30	10–342 (48)
Chronic hepatitis B and C	89	17–73 (43)	55/34	3–55	5	12	26	5–364 (18)
Autoimmune hepatitis and PBC	9	46–71 (55)	2/7	5·5–16	9	12	16	8–149 (66)
Other liver diseases	14	23–76 (59)	10/4	3·2–21	4	9	20	9–298 (41)
Liver transplantation	89	15–75 (53)	48/41	5–90	6	12	33	4–408 (23)

PBC, Primary biliary cirrhosis.

CDT values for moderate drinkers (< 60 g per day) (3–27 units L^{-1}) and those with a daily alcohol intake of more than 60 g per day (3–100 units L^{-1}). The difference between abstinent subjects and chronic drinkers, however, was not significant. Sixty-seven per cent of the chronic drinkers had false-negative CDT values, whereas 11% of the abstinent or moderate users showed false-positive results. More detailed information of distribution of CDT values for all subjects are given in Table 1. We also calculated the clinical use of the CDT test (Table 2) and obtained a significant *P*-value caused by the great number of true-negative test results.

ROC analysis

Figure 2 shows the receiver operating characteristic (ROC) analysis [19] for CDT, γ-GT and MCV for all 405 subjects. As demonstrated, MCV shows the strongest power of discrimination between persons with chronic alcohol abuse and those without, followed by γ-GT and CDT. On the basis of the recommended cut-off concentration for CDT (20 units L^{-1} for men, 26 units L^{-1} for women), CDT showed a diagnostic specificity of 86·9% and a sensitivity of 36·9% for men; for women the specificity was 95% but the sensitivity was 0%. In comparison, the specificity for MCV (cut-off 98 μm^3) was 92·1% for men (sensitivity 25%) and 96·6% for women (sensitivity 50%). γ-GT (cut-off 28 units L^{-1} for men, 18 units L^{-1} for women) showed a specificity of 50·9% and a sensitivity of 80%. For women the specificity was 55·3% and the sensitivity 80%. Our results for MCV and γ-GT are well in agreement with the literature [1,7,21,22]. The evaluation of these results clearly indicates that measurement of CDT is not a useful means to identify chronic drinkers in an unselected population. However, because of much confusion in this matter [8,13,16,23,24] we also analysed separately subgroups of our collective.

Patients with liver diseases

Estimation of chronic alcohol abuse is most important in patients with various liver diseases. In this study, many subjects with various liver diseases and different amounts of alcohol consumption were included (see Table 3). For this

Table 4 Sensitivities and specificities of carbohydrate-deficient transferrin (CDT) for subjects with liver diseases ($n = 213$) in comparison to γ-glutamyltransferase (γ-GT) and mean corpuscular volume (MCV).

	Specificity (%)	Sensitivity (%)	Cut-off
CDT			
Men	83·6	40	20 units L^{-1}
Women	96·9	0	26 units L^{-1}
γ-GT			
Men	36·1	93·1	28 units L^{-1}
Women	36·6	100	18 units L^{-1}
MCV			
Men	89·9	30	98 μm^3
Women	95·7	50	98 μm^3

Table 5 Sensitivities and specificities of carbohydrate-deficient transferrin (CDT) for subjects without liver diseases ($n = 103$) compared with γ-glutamyltransferase (γ-GT) and mean corpuscular volume (MCV).

	Specificity (%)	Sensitivity (%)	Cut-off
CDT			
Men	94·2	34·3	20 units L^{-1}
Women	91·9	0	26 units L^{-1}
γ-GT			
Men	24	89·1	28 units L^{-1}
Women	50	84·7	18 units L^{-1}
MCV			
Men	97·8	20	98 μm^3
Women	98·2	50	98 μm^3

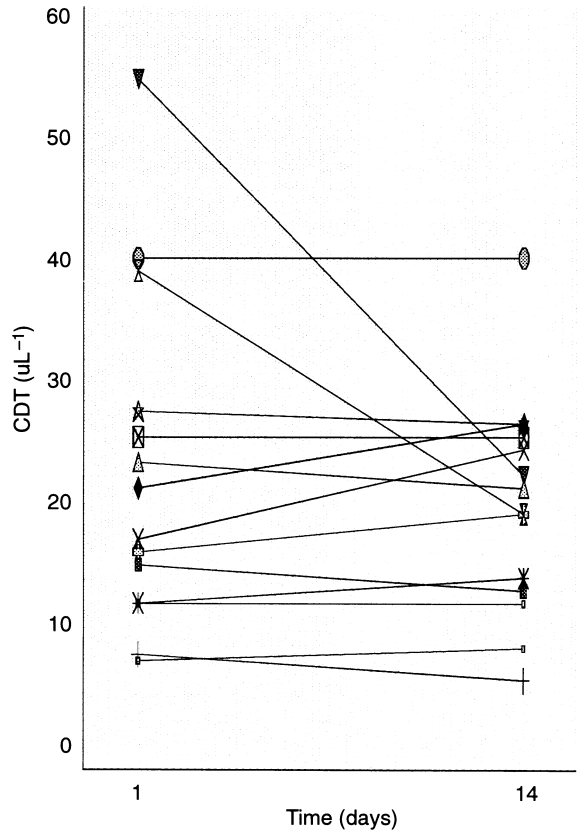

Figure 3 Follow-up investigation for CDT: 14 patients during a follow-up investigation over a period of the first 14 days of alcohol withdrawal.

subgroup the specificity and sensitivity of the CDT test was lower than for the total study group (Table 4).

Patients without liver diseases

As liver diseases may reduce both the specificity and the sensitivity of the CDT test we also calculated our data after exclusion of liver patients. We now obtained a higher specificity, 92·4% for men and 91·9% for women, but an equally low sensitivity (34·3% and 0% for men and women respectively) (Table 5).

Follow-up investigation

The half-life of CDT is approximately 14 days [25] and for transferrin about 8–10 days [1,2,9]. Therefore CDT has been proposed as a useful marker for monitoring alcohol abstinence during withdrawal [24,26]. Fourteen patients with chronic alcohol abuse were followed from the first day of hospitalization for a period of 2–6 weeks. Figure 3 shows the CDT values of all patients for the first 14 days. At the beginning, seven patients had CDT values below the cut-off. Alcohol abstinence was confirmed by measuring the blood alcohol concentration. In only two of the 14 cases a decreased CDT value corresponding to alcohol abstinence was found. For the remainder no significant kinetics was obtained.

Discussion

Several studies have claimed a very high specificity and a high sensitivity of CDT for the detection of chronic alcohol abuse, whereas others discussed its clinical use critically [9,23,27,28]. Nevertheless, a single determination of the CDT concentration to discriminate between drinkers and abstinent persons is widely used in clinical practice and particularly in forensic medicine.

On the basis of our results, we find it important for the discussion about the clinical use of the CDT test to focus on the following questions:

(1) Is a low CDT value able to exclude chronic alcohol abuse?

Among the 405 subjects investigated, 84% had CDT values below the cut-off. Eighty-eight per cent of persons with a daily alcohol intake < 60 g had true-negative test results. As these patients by far formed the largest group of our collective, the chi-square test revealed a significant *P*-value (see Table 2), which, however, does not imply diagnostic use of the test. The *P*-value of the chi-square-test mainly depends on the number of patients, not on the degree of association. Therefore, in differential diagnosis of chronic alcohol abuse in a single patient, the sensitivity and specificity of CDT test are the essential determinants of its use. In the alcohol abuse group, 64% had false-negative CDT values, independent of the presence or absence of liver diseases.

The determination of CDT before surgical intervention as proposed in patients with a high risk of a possible alcohol withdrawal syndrome also turned out to be of no use.

Thus, a low CDT value does not provide valid information regarding chronic alcohol abuse but may instead be misleading.

(2) Is a high CDT value a reliable marker for alcohol abuse?

Among the 65 high CDT test values, we found 26 true-positive and 39 false-positive test results. On the basis of our interviews, we are confident that our patients with high CDT values who deny alcohol abuse are classified correctly. One main reason for a positive CDT value seems to be liver dysfunction (such as liver cirrhosis, fatty liver, chronic hepatitis B and C, cholecystitis and cholecystolithiasis).

Our data also indicate that there is no cut-off value for CDT to exclude liver disease.

(3) Is CDT measurement helpful in the differential diagnosis of patients with elevated γ-GT of unknown origin?

In agreement with others [3,11–14] we demonstrate that the CDT test is a parameter highly influenced by liver diseases. Our data also demonstrate the impossibility to

differentiate further results of general liver parameters, such as the γ-GT or MCV.

(4) Is a CDT test useful in the control of alcohol abstinence?

The determination of CDT in our study did not show any use in the control of withdrawal and abstinence. Seven out of 14 follow-up observations began with CDT values below the cut-off point and showed no concentration kinetics up to 2–6 weeks. In only two of the fourteen cases, a decreased CDT value corresponded to alcohol abstinence.

We conclude that the results of this blinded study on well-defined patients and healthy control subjects underline the insufficient specificity and moreover the very low sensitivity of the CDT test for the detection or exclusion of chronic alcohol abuse. Accordingly, it is not justified to base any medical decision on the measurement of CDT concentrations, this holds even more true for forensic decisions.

Thus, for good clinical practice, measurement of CDT is not recommended.

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