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Comparison of Bio-Rad %CDT TIA and CDTect as Laboratory Markers of Heavy Alcohol Use and Their Relationships with γ-Glutamyltransferase

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Background: **Carbohydrate-deficient transferrin (CDT) is used as a serum marker for heavy drinking. We compared a new Bio-Rad %CDT TIA assay with the CDTect™ assay; we also compared both to γ-glutamyltransferase (GGT) as markers of heavy drinking.**

Methods: **Serum samples of well-defined alcoholics (n = 404) and matched (age, race, and gender) social drinkers (204) from 10 clinical centers were assayed with both CDT assays. Both assays use microcolumn separation after iron saturation, followed by enzyme immunoassay (CDTect) or turbidimetric immunoassay (Bio-Rad %CDT). In the latter, CDT is expressed as a percentage of total transferrin.**

Results: **The slope and intercept [95% confidence intervals (CIs)] for linear regression of results obtained by the %CDT-TIA (as percentage) and CDTect (units/L) assays were 0.091 (0.088–0.097) and 0.70% (0.54–0.86%), respectively ($S_{y|x}$ =1.30%; r = 0.848). The areas under the ROC curves (95% CIs) for CDTect and Bio-Rad %CDT TIA were 0.89 (0.86–0.92) and 0.88 (0.85–0.91), respectively, for men (P, not significant) and 0.76 (0.72–0.80) and 0.72 (0.68–0.76) for women (P, not significant). When CDT (CDTect or Bio-Rad %CDT) was combined with GGT (either one positive), the clinical sensitivity in men was 90% for both assays, and specificities were 81% and 84%, respectively; sensitivities in women were 75% and 76%, respectively, and specificities were 87% and 91%.**

Conclusion: **The new Bio-Rad %CDT TIA assay compares favorably to the widely studied CDTect assay in the detection of alcohol-use disorders.**

Although heavy alcohol use is a ubiquitous problem, many heavy drinkers and alcoholics go undetected. The clinical laboratory is playing an ever-increasing role in assisting with screening and monitoring of heavy alcohol use *(1)*. Since the original report *(2)* more than 15 years ago, many others have indicated that the desialylated form of transferrin, called carbohydrate-deficient transferrin (CDT), is a sensitive and specific marker for heavy alcohol use *(3–5)*. CDT has generally been equally or more clinically sensitive than γ-glutamyltransferase (GGT) but generally more specific *(4, 6)*, especially in individuals with liver disease *(7, 8)*.

Commercial assays have been developed for the measurement of CDT. The widely used and evaluated CDTect™ assay measures specific desialylated forms of transferrin that occur above pI 5.7 and does not correct for total serum transferrin concentration. On the other hand, assays measuring CDT as a percentage of total transferrin *(9)* have been evaluated. Both assays have been compared with more sophisticated, but methodologically complicated, procedures *(4, 10)*. In general, they have compared favorably. Their ease of use makes them the CDT assays of choice for most clinical laboratories. When an older %CDT TIA assay (Axis-Shield ASA, Oslo, Norway) was compared directly with the CDTect assay (Axis-Shield, Oslo, Norway), it was found to be less sensitive but more specific for heavy alcohol intake (range, 3–10 standard drinks/day). On the other hand, when this older %CDT TIA method was compared with an isoelectric focusing/immunoblot/laser densitometry assay, the %CDT procedure yielded better chemical detection characteristics *(10)*. A newer version of the %CDT assay, called the Bio-Rad %CDT TIA assay (Axis-Shield ASA, Oslo, Norway), has recently been developed and approved by the US Food and Drug Administration for commercial use.

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This report used samples collected during a large multisite study to compare the performance characteristics of the CDTect assay and the new Bio-Rad %CDT TIA assay. In addition, a comparison with GGT was made to compare CDT, either corrected (%CDT) or uncorrected (units/L) for total transferrin concentration, with a marker currently in use and to examine the utility of using both markers together.

Materials and Methods

Four hundred forty-four alcoholic individuals (358 males and 86 females) who were recently admitted to alcohol inpatient (detox) units were recruited from 10 clinical centers (see *Appendix*) between July 1996 and February 1998. All 444 individuals met DSM IV criteria for alcohol dependence, but no other substance dependence other than nicotine, and had their blood drawn into red-top glass Vacutainer Tubes within 4 days of their last drinking day. The blood was allowed to clot, and the serum was removed and stored in plastic tubes. Social drinker controls, who matched (age, gender, race) a subsample (n = 204) of the alcoholics, were recruited by advertisement to establish sensitivity and specificity parameters. All participants signed Institutional Review Board-approved informed consents and were interviewed with a sensitive and standard calendar method for daily alcohol consumption over the last 30 days *(11)*. A total of 633 samples (434 from alcoholics, 199 from controls) were available for direct comparison between the CDTect and Bio-Rad %CDT TIA assays. For the data presented here, five alcoholic individuals selected to have matched controls, who had blood analyzed for CDT (units/L), did not have sufficient quantity for reanalysis with Bio-Rad %CDT TIA, leaving a total of 199 alcoholics with matched controls for the sensitivity/specificity analysis.

All blood was shipped to and stored at three reference laboratories (IBT Reference Laboratories, Lenexa, KS; Igenex Inc., Palo Alto, CA; and Clinical Neurobiology Laboratory, Medical University of South Carolina, Charleston, SC) for CDTect analysis (Axis-Shield); one laboratory (Medical University of South Carolina Clinical Neurobiology Laboratories) analyzed all of the samples for Bio-Rad %CDT TIA (Axis-Shield). GGT was assayed in one laboratory (Pharmacia-Upjohn, Kalamazoo MI) by an enzymatic procedure on a Beckman SYNCHRON CX7 automatic analyzer. Reference intervals for the CDTect and GGT assays were set a priori based on the manufacturers' recommendations. The cutoff for the Bio-Rad %CDT TIA assay for sensitivity/specificity analysis was taken as the 95th percentile value (1.65 SD) of the social drinker control population. For the CDTect, values ≥20 units/L for males and ≥26 units/L for females were considered abnormally increased based on the manufacturer's recommendation and on previous literature *(3, 6)*. For the Bio-Rad %CDT TIA assay, values >2.6% were considered abnormally increased. For GGT, values ≥54 U/L for both genders were considered abnormally increased.

Both CDT assays use a microcolumn separation procedure after total iron saturation. In the CDTect assay, only the transferrin moieties with missing sialic acid side chains (asialo, monosialo, and disialo) are separated by microcolumn chromatography from natural transferrin and are expressed as units/L CDT without correction for total transferrin. In the Bio-Rad %CDT TIA assay, which is similar but not exactly the same, sialic-deficient transferrins (asialo, monosialo, and disialo) are separated from the natural transferrin and quantified, and the results are expressed in %CDT (of total transferrin in the sample before column chromatographic separation). In essence, in the latter assay, CDT is calculated in relation to the total amount of transferrin being produced. Each assay uses an antibody to natural transferrin to bind the CDT, but the CDTect assay uses an enzyme immunoassay procedure, whereas the Bio-Rad %CDT TIA uses a turbidimetric immunoassay procedure for quantification. Both assays use calibration curves based on natural (total) transferrin calibrators to quantify the unknown samples. In our hands it took ~7.0 h to run 80 tests with the CDTect assay and ~5 h to run the same number of tests with the Bio-Rad %CDT TIA assay. The intra- and interassay CVs were <8% and <12% for the CDTect and <5% and <8% for the Bio-Rad %CDT TIA assay, respectively.

CDT assays were compared using regression statistics, sensitivity/specificity descriptive analyses, and ROC curves (areas under the curve of the two assays were statistically compared). The sensitivity and specificity of GGT with and without the two CDT measures were also calculated for comparison and to evaluate whether concomitant GGT measurement would enhance the performance of either CDT measure. All assays were performed without knowledge of clinical status.

Results

The demographic and drinking characteristics of the study population are given in Table 1. It is clear that the ages and gender ratios of the matched alcoholic individuals and controls were very well matched and distributed. As in most recently detoxified alcoholic populations, males made up the majority of the population. Oversampling of females for matching with controls produced the type of distribution often found in outpatient alcoholic samples. Alcoholics were drinking on average ~17 drinks/day and drank 27 of the 30 days (90%) before admission. The social drinkers drank on only 3 of the 30 days before sampling, and when they drank, they consumed on average <1 drink/day.

The correlation between the CDTect values and the %CDT values for the whole study population (alcoholics and social drinkers) is shown graphically in Fig. 1. This analysis provided for the broadest comparison of CDT values across the spectrum of results, from the lowest to the highest, with the largest number of individuals (n =

Table 1. Demographic and drinking data of alcoholics with and without matched social drinker controls.[a]

Variables	Alcoholics without matched controls (n = 240)	Alcoholics with matched controls (n = 204)	Controls (n = 204)
Age, years	44 ± 10	44 ± 10	44 ± 10
Gender, %			
Males	93	67	67
Females	7	33	33
Race, %			
Caucasian	70	82	82
African-American	30	17	17
Other		1	1
In past 30 days			
Drinks per day	17 ± 10	16 ± 12	0.2 ± 0.3
Days drinking	27 ± 5	26 ± 6	3 ± 6

[a] Data given as mean (± SD) or percentage.

633). There was a strongly positive correlation ($r = 0.848$) between the two assays, which was highly significant ($P < 0.0001$). Because the correlation was not perfect, an evaluation of the most discrepant points (outliers) was undertaken to further illustrate reasons for assay differences. The Bio-Rad %CDT values, CDTect values, and total transferrin values (obtained from the Bio-Rad test assay) for those samples that were the most discrepant are presented in Table 2. As can be seen, the total transferrin values (mean, 2490 ± 1050 mg/L) in the samples where %CDT was low and CDTect was high were higher than the total transferrin values (mean, 1180 ± 700 mg/L) where %CDT was high and CDTect was low. This total transferrin difference was significantly different ($t = 3.2$; $P < 0.01$). As a point of reference, the mean total transferrin for the entire sample was 1960 ± 700 mg/L.

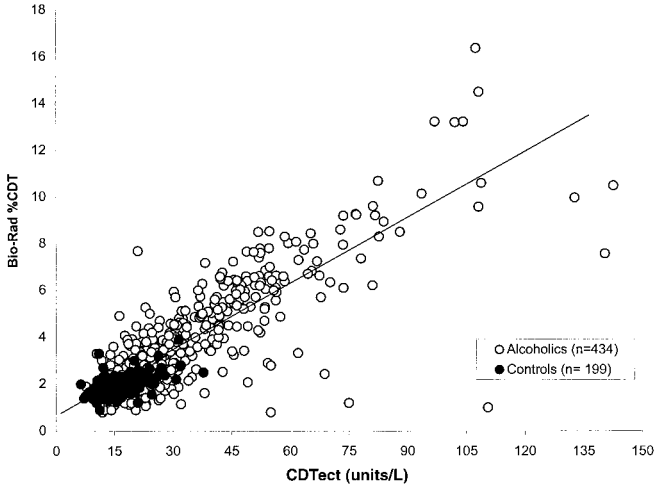

Fig. 1. Correlation between Bio-Rad %CDT TIA and CDTect values in alcoholics (○; n = 434) and social drinking controls (●; n = 199).

The slope and intercept of the regression between the two assays (with 95% confidence intervals) are 0.091 (0.088–0.097) and 0.70% (0.54–0.86%), respectively ($S_{y|x} = 1.30\%$; $r = 0.848$).

The relationship between the CDTect and the %CDT results by gender for alcoholics alone is provided in Table 3. In addition, how these tests relate to GGT concentrations is also provided. It is clear that although there was a highly significant correlation between the two CDT assays for both male ($P < 0.01$) and female ($P < 0.01$) alcoholics, the actual correlation in males was somewhat stronger but no less statistically significant. Of note, neither assay was strongly correlated with GGT in either gender.

ROC plots comparing CDTect values with %CDT values for men and women independently are given in Fig. 2. The areas under the ROC curves were similar for the CDTect and Bio-Rad %CDT TIA for both men (0.888 vs 0.882; $P = 0.67$) and women (0.764 vs 0.721; $P = 0.26$).

The actual sensitivities and specificities for CDTect, %CDT, and GGT (with and without either of the CDT values) are given in Table 4 for each gender. The actual numbers of individuals are available in a data supplement published in the online version of this article (available at *Clinical Chemistry Online*, http://www.clinchem.org/content/vol47/issue10). For the combined CDT and GGT calculations, if a person had a value greater than the cutoff for either the CDT test or the GGT test, that individual was considered positive. If a person had a value below the cutoff for both the CDT test and the GGT test, that individual was considered negative. As mentioned previously, the cutoff (2.6%) for %CDT was based on the 95th percentile for the social drinking (control) population. It is not surprising, therefore, that the specificity for %CDT was actually 96% in males and 94% in females. The specificities for the other analyses were derived from the cutoff values established historically for CDTect and GGT, respectively.

It appears that both CDT assays gave similar sensitivities in men, but with somewhat lower specificity for the CDTect assay. On the other hand, the %CDT assay provided greater sensitivity with higher specificity in women. However, it should be noted that, in general, both CDT assays performed better in males than females overall. For males, both CDT assays performed better than GGT for both sensitivity and specificity. For females, however, there was less difference between GGT and CDT, especially for the %CDT, which exhibited sensitivity and specificity characteristics similar to those for GGT.

When either CDTect or Bio-Rad %CDT TIA was combined with GGT (when either one or the other was positive), the sensitivity noticeably increased without an excessive drop in specificity. This was particularly noteworthy in women.

Discussion

The main purpose of this study was to evaluate two CDT assays for performance when the clinical data are well controlled to minimize population variability and enhance clinical data validity. In fact, one might argue for biologic markers of alcohol use that this is the only way to effectively evaluate assay differences given the notorious

Table 2. Most discrepant values between Bio-Rad %CDT TIA and CDTect in relation to total transferrin serum.

	Type	Sex	Bio-Rad %CDT	CDTect, units/L	Total transferrin, mg/L
Participants with low %CDT but high CDTect					
	Alcoholic	M	1.2	75.0	1810
	Alcoholic	M	2.1	49.1	1510
	Alcoholic	F	1.6	38.0	2850
	Alcoholic	M	1.6	30.2	4650
	Alcoholic	M	2.5	42.7	2860
	Alcoholic	M	1.0	110.5	2590
	Alcoholic	M	0.8	55.0	2410
	Alcoholic	M	2.4	68.8	2800
	Social drinker	F	2.5	37.8	940
	Mean (SD)				2490 (1050)[a]
Participants with high %CDT but low CDtect					
	Alcoholic	F	3.0	14.5	610
	Alcoholic	M	2.7	12.7	2540
	Alcoholic	M	3.0	11.8	1100
	Alcoholic	M	3.3	10.4	770
	Alcoholic	M	2.7	13.7	760
	Alcoholic	M	2.6	13.5	480
	Alcoholic	F	3.6	14.8	1920
	Alcoholic	F	4.9	16.3	1840
	Social drinker	M	3.3	11.0	1240
	Social drinker	M	2.7	12.1	520
	Mean (SD)				1180 (700)[a]

[a] Significant difference between group means: t = 3.2; *df*, 17; $P < 0.01$.

underreporting of alcohol use that occurs in many clinical settings. This study used many participants from several different clinical sites, which should make the results more generalizable and interpretable. Drinking data were obtained by experienced alcohol researchers using state-of-the-art and widely tested interview methods. The alcoholic individuals were carefully selected and contrasted with carefully matched social drinkers. Although the performance of the assays can be more ideally contrasted under these conditions, the sensitivity and specificity are nevertheless optimized. In fact, it has been recognized previously that the sensitivity and specificity of CDT will vary according to the population under study *(3)*. In general, this reflects the variability of the drinking levels in clinical vs nonclinical populations. One must take this into account in interpreting the results of these tests. It also should be noted that individuals selected for this study were medically stable and did not have severe liver pathology, which could affect the specificity of these assays *(12)*. In general, CDT has been found to be more specific for heavy alcohol use in individuals with hepatic disease than GGT *(7, 8)* and to perform well in general acute medical clinics *(13)*.

The main purpose of this report was to compare assay parameters in populations representing the most clearly definable conditions. In this context, it is clear that the Bio-Rad %CDT TIA assay performs equally well, if not better, than the older, more widely used CDTect assay. Although both assays produced highly correlated results, the Bio-Rad %CDT TIA had the same 95% cutoff for men and women, which has not historically been the case with the CDTect assay. Moreover, the Bio-Rad %CDT TIA assay appeared to perform marginally better than CDT in females. It is likely that accounting for CDT as a percent-

Table 3. Correlation coefficients (*r*) for CDTect (units/L), Bio-Rad %CDT TIA, and GGT in the alcoholics, by gender.

	Males		Females	
	CDTect, units/L	Bio-Rad %CDT TIA	CDTect, units/L	Bio-Rad %CDT TIA
Bio-Rad %CDT TIA	0.87[a]		0.70[a]	
GGT	−0.13	−0.10	0.07	0.17

[a] $P \leq 0.01$.

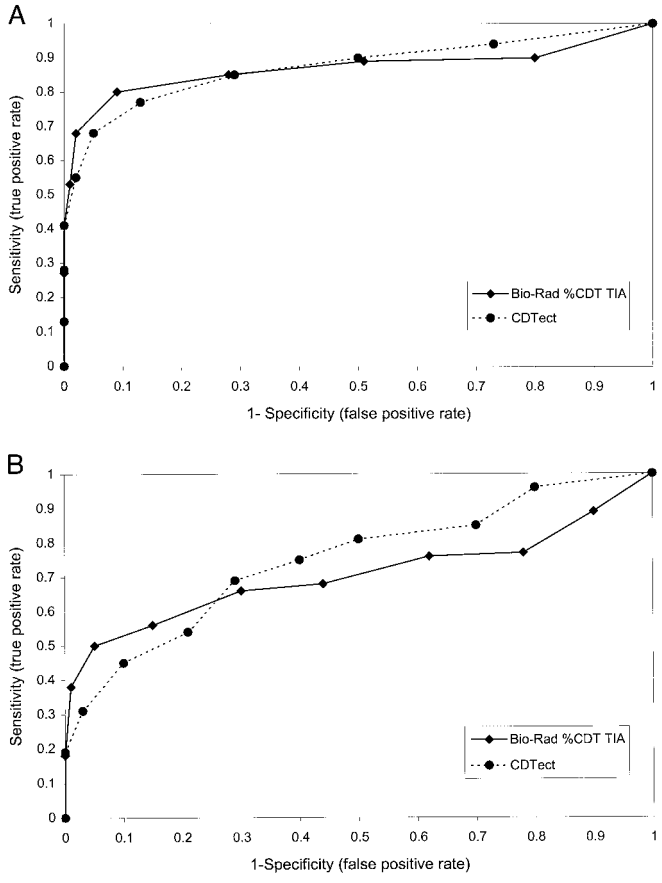

Fig. 2. ROC curves for comparison of the performance of the Bio-Rad %CDT TIA (♦) and CDTect (●) in the identification of alcoholic men (*A*) and women (*B*).

The areas under the curves (with 95% confidence intervals) were 0.88 (0.85–0.91) and 0.89 (0.86–0.92) for men ($P = 0.67$) and 0.72 (0.68–0.76) and 0.76 (0.72–0.81) for women ($P = 0.26$), respectively.

age of total transferrin (%CDT) may be taking into account natural variability in transferrin concentrations present in women, possibly secondary to iron deficiency *(14)* or hormonal effects *(15)*. In this context it was informative to evaluate the most discrepant values between the two assay conditions. Independent of gender and diagnostic status, it appeared that the total serum transferrin content may have played a role in many discrepancies (Table 2). In general, it appeared that when total transferrin was low, the %CDT assay gave relatively higher values than the CDTect assay, but when total transferrin was high, the Bio-Rad %CDT assay gave relatively lower values than the CDTect assay. The reasons for this are not readily apparent, and it does not account for the total discrepancy because several total transferrin concentrations in both groups overlapped with those in the other and many, of course, overlapped with transferrin concentrations found in nondiscrepant values. Undoubtedly, in a sample of this size, some technical variability will appear, leading to some discrepancy in assay performance.

These results support, as suggested previously *(4, 6)*, that CDT is not highly correlated with GGT and therefore may be used as independent markers of heavy alcohol consumption. CDT measurement by either method had marginally better detection performance than GGT in males, but not in females. However, when the results were used conjointly (either one or the other positive), the sensitivity for heavy alcohol use went up markedly for both genders without a large decline in specificity.

Others have compared assays of similar characteristics. For example, Viitala et al. *(9)* compared a similar %CDT assay to the one reported here with the CDTect assay in 90 heavy drinkers consuming on average 35–143 g/day (3–10 standard drinks/day). These heavy drinkers were compared with social drinkers and hospital patients with abnormal transferrin concentrations (both low and high). They found that CDTect was, in fact, more sensitive for the detection of heavy drinking, especially for men, but that %CDT was more specific for heavy drinking, especially when compared in patients with abnormal serum transferrin concentrations. In our study with heavy drinkers, we found no such difference in sensitivity between the new Bio-Rad %CDT TIA assay and the CDTect. However, the specificity conclusions in our study are limited because our participants were relatively healthy except for chronic alcoholism.

Table 4. Sensitivity and specificity (95% confidence intervals) for CDTect (units/L), Bio-Rad %CDT TIA, and GGT at the specified cutoffs for males and females.[a]

	Males		Females	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**
CDTect,[b] (units/L)	0.73 (0.65–0.80)	0.91 (0.85–0.95)	0.41 (0.29–0.54)	0.90 (0.80–0.96)
Bio-Rad %CDT TIA[c]	0.73 (0.68–0.78)	0.96 (0.92–0.99)	0.52 (0.42–0.63)	0.94 (0.88–1.00)
GGT[d]	0.65 (0.57–0.73)	0.89 (0.82–0.94)	0.54 (0.42–0.67)	0.97 (0.90–1.00)
CDTect (units/L) with GGT	0.90 (0.84–0.95)	0.81 (0.73–0.87)	0.75 (0.63–0.85)	0.87 (0.76–0.94)
Bio-Rad %CDT TIA with GGT	0.90 (0.87–0.93)	0.84 (0.78–0.90)	0.76 (0.67–0.85)	0.91 (0.84–0.98)

[a] Based on 199 alcoholics (132 males and 67 females) and 199 matched social drinkers.
[b] CDTect cutoffs are 20 units/L for men and 26 units/L for women.
[c] Bio-Rad %CDT TIA cutoff is 2.6% for both men and women.
[d] GGT cutoff is 54 U/L for both men and women.

This study was limited to the evaluation of the two CDT assays in a cross-sectional, screening, or detection evaluation. CDT has also been used to "monitor" alcoholics during treatment and recovery [Refs. *(16–19)*, and Anton RF, Lieber C, Tabakoff B, and the CDTect Study Group. Carbohydrate deficient transferrin (CDT) and γ-glutamyltransferase for the detection and monitoring of alcoholics. Results from a multi-site study (under review)]. It has been suggested by several authors [Refs. *(16, 17)*, and Anton RF, Lieber C, Tabakoff B, and the CDTect Study Group. Carbohydrate deficient transferrin (CDT) and γ-glutamyltransferase for the detection and monitoring of alcoholics. Results from a multi-site study (under review)] that monitoring the change in CDT over time is more useful than periodic individual measurements for monitoring abstinence and detecting relapse drinking. Our group *(20)* has recently evaluated the Bio-Rad %CDT TIA assay in this regard and found it to be at least as sensitive as the CDTect *(17)*.

In conclusion, the new Bio-Rad %CDT TIA assay shares similar performance characteristics with the older CDTect assay. It is more time-efficient to perform and may be more specific for alcohol-use disorders. Studies in various types of patients with acute and chronic medical illnesses are needed. Performance characteristics of the new assay in general medical and primary care clinics also need to be evaluated. It must be kept in mind that the conditions under which this study was conducted were set to optimally evaluate the measurement characteristics of the assays. Various research and clinical populations will differ, and the assays may show characteristics different from those reported here. It should also be remembered that these tests are far from perfect. Clinical correlations are mandatory, including the use of good histories, physical exams, and screening questionnaires for alcohol-use disorders *(21)*. Nevertheless, measurement of CDT should provide a tool for clinical laboratories to assist the clinician in assessment of alcohol-use disorders.

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