0145-6008/02/2603-0332$03.00/0
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 26, No. 3
March 2002

CDT, GGT, and AST As Markers of Alcohol Use: The WHO/ISBRA Collaborative Project

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Background: Estimates of the performance of carbohydrate deficient transferrin (CDT) and gamma glutamyltransferase (GGT) as markers of alcohol consumption have varied widely. Studies have differed in design and subject characteristics. The WHO/ISBRA Collaborative Study allows assessment and comparison of CDT, GGT, and aspartate aminotransferase (AST) as markers of drinking in a large, well-characterized, multicenter sample.

Methods: A total of 1863 subjects were recruited from five countries (Australia, Brazil, Canada, Finland, and Japan). Recruitment was stratified by alcohol use, age, and sex. Demographic characteristics, alcohol consumption, and presence of ICD-10 dependence were recorded using an interview schedule based on the AUDADIS. CDT was assayed using CDTect™ and GGT and AST by standard methods. Statistical techniques included receiver operating characteristic (ROC) analysis. Multiple regression was used to measure the impact of factors other than alcohol on test performance.

Results: CDT and GGT had comparable performance on ROC analysis, with AST performing slightly less well. CDT was a slightly but significantly better marker of high-risk consumption in men. All were more effective for detection of high-risk rather than intermediate-risk drinking. CDT and GGT levels were influenced by body mass index, sex, age, and smoking status.

Conclusions: CDT was little better than GGT in detecting high- or intermediate-risk alcohol consumption in this large, multicenter, predominantly community-based sample. As the two tests are relatively independent of each other, their combination is likely to provide better performance than either test alone. Test interpretation should take account sex, age, and body mass index.

Key Words: Biological Markers, Diagnosis, Carbohydrate Deficient Transferrin, Gamma Glutamyltransferase, Biochemistry.

MANY PAPERS HAVE reported on the performance of carbohydrate deficient transferrin (CDT) or gamma glutamyltransferase (GGT) as markers of excessive alcohol consumption (Allen et al., 1994; Mundle et al., 2000; Reynaud et al., 2000). These markers are potentially important for both the detection and monitoring of patients with alcohol dependence and for the early detection of nondependent hazardous or harmful drinking. Accurate identification of drinking problems has increased in importance because of the body of evidence for the effectiveness of both early intervention techniques and of pharmacotherapy for alcohol dependence.

CDT has generally been found to perform better than other markers of alcohol consumption, such as the liver enzymes GGT and aspartate aminotransferase (AST), in detecting heavy alcohol consumption or alcohol-use disorders (Allen et al., 1994). In some cases, this may reflect the poorer specificity of GGT or AST in patients who may have liver disease. Early reports of CDT's sensitivity and specificity were often above 90%, (Stibler, 1991) but later studies have suggested lower accuracy. Sensitivity has been as low as 20% in community samples (Lof et al., 1994; Nystrom et al., 1992) and specificity below 65% in some clinical samples (Xin et al., 1992). Some of the variation may be explained by differences in the severity of alcohol problems or prevalence of liver disease in the samples, but the span of results remains considerable. It is difficult to compare estimates of test performance from different studies, because study design and subject characteristics vary as do assay methods, thresholds used to define excessive drinking, and test cutoffs (Scouller et al., 2000). Meta-analysis can help examine factors that influence marker levels, but issues of the validity of pooling data arise.

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Received for publication April 4, 2001; accepted December 6, 2001.

This research was supported by the Banbury Foundation; NIAAA; WHO/ISBRA; and, in Australia, by the National Health and Medical Research Council.

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CDTect™ kits were supplied by Pharmacia Diagnostics, Uppsala, Sweden; and by Axis Biochemicals, Oslo, Norway.

The WHO/ISBRA Study on State and Trait Markers of Alcohol Use and Dependence was established in 1988 to assess and compare markers of recent alcohol use and also of the trait of alcohol dependence in a multicenter trial (Helander and Tabakoff, 1997; Menninger et al., 2000). The study group incorporated representatives from the World Health Organization, the International Society for Biomedical Research on Alcoholism (ISBRA), and the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Here we report on the performance of CDT, GGT, and AST in this large, multicenter international study. We also examine whether factors such as age, sex, body mass index (BMI), and country of recruitment influence response of these markers to alcohol consumption and assess whether the markers are as useful in nonalcohol-dependent as in alcohol-dependent persons.

METHODS

Sample

Subjects aged 18 and over were recruited in five countries: Australia (Sydney), Brazil (São Paulo), Canada (Montreal), Finland (Helsinki), and Japan (Sapporo). A range of recruitment settings was used but primarily included the community and alcohol dependence treatment services. General hospital inpatients were not recruited. In each center, recruitment was stratified by age and alcohol consumption categories (including nondrinkers, current drinkers, and persons currently receiving treatment for alcohol dependence) (Helander et al., 1997; Menninger et al., 2000) and, where both male and female subjects were recruited, by sex. In Australia and Finland, only men were recruited. In most centers, convenience (nonrandom) sampling was used and, in some centers, volunteers were recruited by advertisements.

Patients resident in alcohol dependence treatment units were interviewed within 72 hr of admission. Subjects were excluded if they had major medical and psychiatric disorders (e.g., any medical condition or complication of drinking requiring hospitalization in its own right; psychosis), if they reported intravenous drug abuse, were being treated for dependence on a substance other than alcohol, or had received disulfiram treatment in the past month. Except for the nondrinkers group, patients were excluded if they had not had a drink containing alcohol in the past month.

Interview

The WHO/ISBRA Interview Schedule was adapted from the Alcohol-Use Disorders and Associated Disabilities Interview Schedule (AUDADIS) developed by the NIAAA (Grant and Harford, 1990; Grant et al., 1995). It gathers a range of data including sociodemographic details, self-reported weight and height, frequency and quantity of beverage-specific alcohol consumption during the past 30 days, and symptoms of alcohol-use disorders (Menninger et al., 2000). Diagnosis of alcohol dependence according to ICD-10 criteria can be extracted. The reliability of the AUDADIS has previously been demonstrated (Grant et al., 1995). The schedule was translated into Finnish, Japanese, French, and Portuguese for the purpose of this study, and accuracy of translation was checked by back-translation.

Blood Samples

Blood samples were collected at the time of the interview. After local processing, samples were frozen and shipped to Helsinki, where plasma was sent for GGT and AST assay at the laboratories of ALKO and KTL (Helsinki, Finland), and serum was sent for CDT assay at the Alcohol Laboratory (Stockholm, Sweden) (Menninger et al., 2000).

Table 1. Demographics of the Cohort According to Gender

	Males		Females	
	%	(*n*)	%	(*n*)
	67	(1250)	33	(613)
Age group				
18–30	31	(383)	34	(209)
30–39	27	(331)	22	(137)
40–49	23	(292)	23	(140)
50+	20	(244)	21	(127)
Recruitment site				
Helsinki	19	(235)	—	—
Sydney	23	(285)	—	—
Sapporo	8	(100)	14	(84)
São Paulo	25	(317)	39	(237)
Montreal	25	(313)	48	(292)
Drinking category[1]				
Low risk	57	(713)	62	(380)
Intermediate risk	18	(219)	7	(42)
High risk	26	(318)	31	(191)
ICD-10 alcohol dependence				
Ever	50	(618)	37	(227)
Past year	37	(463)	29	(177)
Other drug use				
Tobacco use past month	48	(597)	45	(275)
Cannabis use in past month	14	(168)	13	(79)
Cocaine use in past month	5	(65)	5	(32)

1. Male low risk: less than or equal to 40 g of alcohol per day; intermediate risk: >40 and up to 80 g of alcohol per day; high risk: >80 g of alcohol per day.
Female low risk: less than or equal to 20 g of alcohol per day; intermediate risk: >20 g and up to 40 g of alcohol per day; high risk: >40 g of alcohol per day.

GGT and AST were assayed by reflectance spectrophotometry using a Vitros 250 Analyser (Ortho Clinical Diagnostics, Rochester, NY). Serum CDT determinations were carried out in duplicate using the CDTect™ test, which employs separation of transferrin isoforms on an anion exchange chromatography microcolumn followed by quantification by a double antibody radioimmunoassay. In this method, the CDT content is expressed as an absolute amount (in U/liter, where 1 U refers to ~1 mg transferrin) of the transferrin isoforms with a pI > 5.7 (i.e., a-, mono- and part of disialo transferrin). CDT levels of more than 20 U/liter for men and more than 26 U/liter for women were considered elevated, in accordance with manufacturer's instructions. GGT and AST levels of more than 40 U/liter were considered elevated, for both men and women.

Statistical Analysis (Correlations, Sensitivity, and Specificity)

Correlations between average daily alcohol consumption and each of the laboratory marker levels were calculated for the whole sample and for men and women separately. Because of the positively skewed distribution of the raw data, log-transformed values of markers and of alcohol consumption were used for correlation and regression analyses. To assess any correlation between CDT and GGT that might be unrelated to alcohol consumption, the partial correlation between markers, adjusting for current alcohol intake, was also calculated.

The sensitivity and specificity of the tests were calculated for detecting intermediate-risk and high-risk drinking in men and in women. Commonly used laboratory cutoffs were used (see above). For the purposes of analysis, levels of risk for men and women were defined as described in Table 1. The consumption thresholds for intermediate risk were chosen to reflect levels at which hazards of drinking begin to increase (National Health and Medical Research Council, 1992). The thresholds for high risk were chosen to reflect levels at which physical harm becomes likely.

ROC Analyses

Receiver operating characteristic (ROC) analysis was used to assess the performance of markers across the full range of potential cutoff values (Coombs et al., 1970). ROC curves plot a scale's ability to detect true

Table 2. Correlation Between CDT, GGT, AST, and Average Daily Alcohol Consumption for Men and for Women

	Average daily alcohol consumption	CDT	GGT	AST
Average daily alcohol consumption	—	0.27	0.37	0.24
CDT	0.46	—	0.03 (ns)	0.13 ($p = 0.002$)
GGT	0.38	0.27	—	0.61
AST	0.34	0.37	0.68	—

Female results are shown above the diagonal (in the shaded cells), and male results below. All correlations are $p < 0.001$ unless otherwise indicated.

positives (e.g., persons correctly classified as problem drinkers) against the rate of false positives (e.g., persons incorrectly classified as problem drinkers). The area under the ROC curve is used as a measure of overall test accuracy. This is a summary measure of a scale's ability to discriminate between affected and unaffected persons. Perfect discrimination is indicated by a score of 1.0 and chance performance by a score of 0.5.

ROC curves were calculated separately for men and women. For each marker (CDT, GGT, and AST), separate ROC analyses were conducted comparing those drinking at intermediate-risk levels against those with low-risk consumption and those drinking at high-risk against those at low-risk levels. The significance of the difference between the area under the curve (AUC) for two markers was compared using DeLong's method (1988). This takes into account pairing of the test data (i.e., that CDT, GGT, and AST results can be compared for each individual).

Multivariate Regression

To examine other potentially significant predictors of CDT, GGT, and AST levels, a multivariate analysis was conducted, including the following predictor variables: average daily alcohol consumption (grams) in the past month, lifetime diagnosis of ICD-10 alcohol dependence, age, sex, smoking status (nonsmoker, ex-smoker, current smoker), BMI, race (Black, Asian/Indian, White, other), and recruitment site. The effect of any psychoactive drug used by more than 5% of the sample was also examined.

To examine possible interactions, average marker levels were plotted against mean daily alcohol consumption according to:

1. lifetime diagnosis of ICD-10 alcohol dependence;
2. BMI, grouped as follows: <20; 20–24.99; 25–29.99; and ≥30 kg/m^2. The top two categories correspond to US National Institute of Health classifications of overweight and obese (US National Institute of Health, 1998);
3. age group (under 20 years; 20-34; 35-49; 50 and over);
4. recruitment site (Helsinki, Montreal, São Paulo, Sapporo, and Sydney).

All analyses were conducted using SPSS for Windows, Version 10 (SPSS Inc, Chicago, IL).

RESULTS

Characteristics of the Sample

The sample comprised 1863 subjects, of which 1250 (67%) were male. The drinking level and other characteristics of the sample are described in Table 1. Even though only 8.5% were recruited from an alcohol dependence treatment center, almost half the subjects (45%) had met criteria for ICD-10 alcohol dependence at some stage in their life, and one third (34%) met criteria for dependence within the past year. While 13% of subjects used cannabis and 5% used cocaine in the past month, less than 2% used each of the following drugs: sedatives, tranquilizers, pain killers, stimulants, or hallucinogens. Less than half of one percent used heroin or methadone, or abused inhalants, and no subject reported anabolic steroid use.

Liver disorders (enlarged liver, cirrhosis, or hepatitis) had been experienced in the past by 9.6% subjects (5% of those drinking 3–40 g/day; 9.5% of those drinking 40.01–80 g/day; and 22.3% of those drinking >80 g/day).

In subjects drinking >40–80 and >80 g/day of ethanol, blood was taken a mean of 1.8 and 2.8 days, respectively, after the last drink (standard error of 0.1 days each). Only 1% of subjects drinking >40 g/day had blood taken more than 14 days after the last drink.

Correlations Between CDT, GGT, AST, and Daily Alcohol Consumption

In men, the correlation between marker levels and alcohol consumption was strongest for CDT ($r = 0.46$), followed by GGT, then AST (Table 2). In contrast, in women, GGT was a stronger correlate of alcohol consumption than CDT ($r = 0.37$ and 0.27, respectively), which performed only slightly better than AST ($r = 0.24$).

In men, the correlation between CDT and GGT levels was 0.27 ($p < 0.001$) but, in women, the correlation did not reach statistical significance ($p = 0.03$). When alcohol consumption was statistically controlled, the correlation between CDT and GGT became weak and marginally significant for men (partial correlation = 0.07, $p < 0.05$) and nonsignificant for women (partial correlation = -0.08).

Sensitivity and Specificity of Elevated CDT and GGT Levels in Detecting High-Risk Alcohol Use

At the chosen laboratory cutoffs, CDT was more specific but less sensitive than GGT in detecting high-risk alcohol consumption (as defined above). Both CDT and GGT were more sensitive in detecting high-risk alcohol use among men (60% and 67% sensitivity, respectively) than among women (29% and 44%). CDT provided good specificity for this level of consumption in both men and women, while GGT yielded greater specificity among women than among men (Table 3). AST was a less sensitive and more specific test than GGT and CDT in both men and women.

The combined use of GGT and CDT, where a positive result in either test constitutes an overall positive result (CDT and/or GGT), was associated with increased sensitivity compared with either test alone, but with some loss of specificity (Table 3). In men, the specificity fell below 70% for the combination of tests, while in women it remained above 80%.

Table 3. Sensitivity and Specificity of Elevated CDT and GGT Levels in Detection of High-Risk Drinking in the Past Month by Sex[1]

	Men (>80 g per day)		Women (>40 g per day)	
	Sensitivity	Specificity	Sensitivity	Specificity
CDT	60	92	29	92
GGT	67	74	44	90
AST	45	90	23	97
CDT and/or GGT	86	68	61	81

1. Persons drinking at intermediate risk levels were excluded from this analysis.

Elevated CDT levels were defined as greater than 26 U/L for women and greater than 20 U/L for men; elevated GGT or AST levels were defined as greater than 40 U/L for both men and women.

ROC Analyses

Among men, all three markers performed better in detection of high-risk drinking (>80 g/day) than intermediate-risk drinking (>40–80 g/day) (Fig. 1).

Among men, CDT performed slightly but significantly better in detecting high-risk drinking than either GGT or AST ($p = 0.02$ and 0.001, respectively). In contrast, for intermediate-risk drinking among men, CDT was not a significantly better test than GGT ($p = 0.58$), though it remained significantly better than AST ($p = 0.02$).

A different pattern was found for women. High-risk consumption tended to better detected by GGT than by CDT, though the difference in performance was not significant ($p = 0.20$). CDT still performed significantly better than AST ($p = 0.004$). None of the markers performed well in detecting intermediate-risk consumption in women: GGT performed at a level only slightly better than chance (95% CI, 0.52–0.71); neither CDT nor AST performed significantly better than chance.

CDT performed less well in women than in men at both intermediate-risk and high-risk levels. To determine whether this was due to the lower alcohol consumption thresholds used for defining these categories in women, CDT's performance in detecting drinking at a level of 60–90 g/day in men and in women was examined (excluding those with higher level consumption). There were 133 men and 44 women drinking 60–90 g/day of ethanol. CDT's performance was not significantly different between men and women in this scenario (men: AUC 0.64, 95% CI, 0.59–0.68; women: AUC 0.61, 95% CI, 0.52–0.70), suggesting that CDT may be just as responsive among women, given similar levels of alcohol intake. At this level of consumption, CDT was not a significantly better marker than GGT in either men or women ($p = 0.10$ and $p = 0.08$, respectively).

Other Factors That Influence Marker Levels

Age Group. Among those aged less than 20 ($n = 77$), alcohol consumption showed minimal association with CDT or GGT levels (Fig. 2). In contrast, in older subjects, CDT and GGT levels increased with increasing average daily alcohol consumption. The patterns for AST were similar to those of GGT.

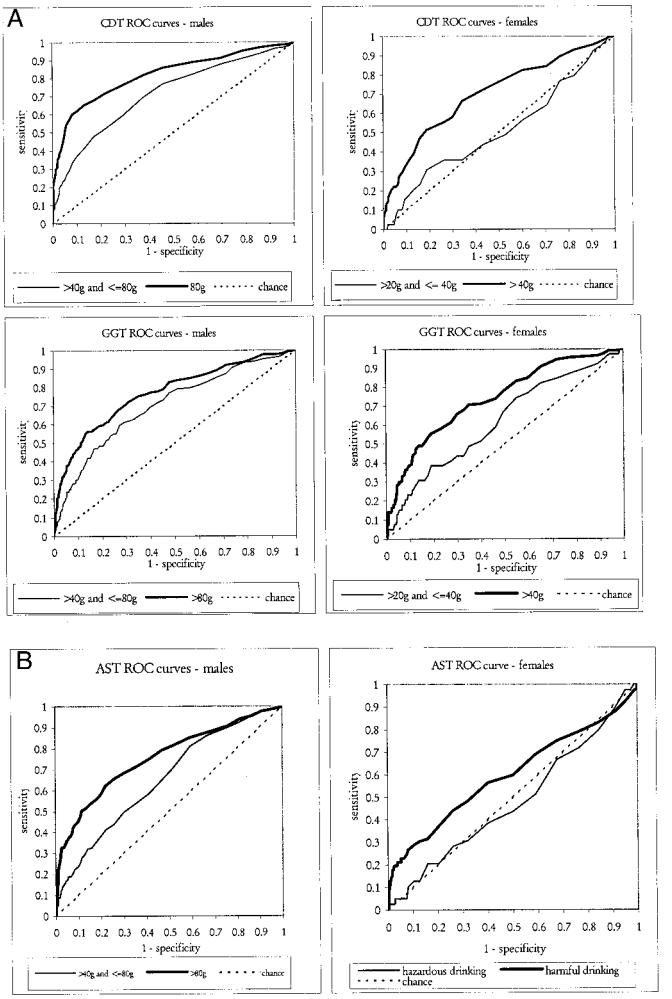

Fig. 1. ROC curves of the performance of CDT, GGT, and AST in detecting intermediate-risk and high-risk alcohol use by sex. (1) In ROC analyses for intermediate-risk drinking, those with high-risk drinking were excluded; in analyses for high-risk drinking, those with intermediate-risk drinking were excluded. (2) The area under the curve and 95% confidence interval [AUC (95% CI)] for the above curves are: for CDT in men: intermediate risk = 0.71 (0.67–0.75), high risk = 0.82 (0.79–0.85); for CDT in women: intermediate risk = 0.51 (0.41–0.61), high risk = 0.70 (0.65–0.75); for GGT in men: intermediate risk - 0.70 (0.66–0.74), high risk - 0.77 (0.74–0.80); for GGT in women: intermediate risk - 0.62 (0.52–0.71), high risk = 0.74 (0.70–0.79); for AST in men: intermediate risk = 0.65 (0.61–0.69), high risk = 0.75 (0.72–0.79); for AST in women: intermediate risk = 0.48 (0.38–0.58), high risk = 0.60 (0.54–0.65).

Body Mass Index (BMI). High BMI was associated with increased GGT levels, particularly in the highest alcohol consumption category (Fig. 3). In contrast, the response of CDT to alcohol use appeared greater in lean subjects.

Country of Recruitment. Bivariate analysis indicated a tendency for subjects recruited from the Japanese site to have lower CDT levels for the same level of alcohol consumption, while those recruited from São Paulo tended to have higher liver enzyme (GGT and AST) levels.

Multivariate Analysis

Using multiple regression analysis, a number of variables were examined as possible predictors of CDT, GGT, and

AST levels (Table 4). Age remained a significant predictor of the level of each marker. Men tended to have higher GGT and AST levels for the same alcohol consumption level, while women tended to have higher CDT levels. As with bivariate analysis, BMI was associated with higher GGT levels but lower CDT levels. There was a tendency ($p < 0.05$) for Whites to have lower GGT levels than other races. Subjects from Montreal and Sydney tended to have lower CDT levels ($p < 0.05$). The lower CDT levels seen for Sapporo on bivariate analysis were no longer significant on multivariate analysis. Subjects from Montreal also tended to have lower AST levels ($p < 0.05$). As with the bivariate analysis, subjects from São Paulo had higher liver enzyme levels.

A diagnosis of ICD-10 alcohol dependence at any stage in the life was positively associated only with AST levels on multivariate analysis. Subjects who met criteria for dependence in the past year had significantly higher marker levels for CDT, GGT, and AST, even after controlling for average alcohol intake in the past month and lifetime alcohol dependence.

As BMI, age, and sex were all predictive of marker levels, and each are determinants of total body water (TBW), additional regression analyses were undertaken to assess whether their effect on marker levels was mediated via their effect on TBW. This is plausible, because TBW determines the volume of distribution of alcohol and hence affects blood alcohol levels. When TBW was added as an independent variable in addition to those shown in Table 4, it was found to be a significant predictor of CDT levels ($\beta = -0.39$), with higher TBW levels predicting lower CDT levels. Sex and BMI remained significant predictors of CDT levels, but age was no longer a significant predictor. In contrast, for both GGT and AST, TBW was not a significant predictor of marker levels, and age, sex, and BMI remained significant predictors.

As expected, a history of liver disease was a highly significant predictor of GGT and AST levels after controlling for the other predictors examined in Table 4 ($\beta = 0.19$ and 0.11, respectively; $p < 0.001$), but liver disease was not a predictor of CDT levels ($p = 0.72$). History of having smoked cigarettes in the last month was associated with slightly higher CDT and GGT levels ($\beta = 0.06$ each; $p < 0.05$). Neither cocaine nor cannabis use affected CDT or GGT levels ($p > 0.05$).

DISCUSSION

The WHO/ISBRA study provided a unique opportunity for examination of biological markers of alcohol use in different countries and among subjects with a range of alcohol consumption levels. The study documents the performance of CDT, GGT, and AST in 1863 subjects and the relationships with age, sex, and BMI. All three markers were found to have limited performance in the detection of intermediate- or high-risk drinking. When the tests were compared using a summary measure of test performance (area under the ROC curve), CDT performed only slightly better than GGT in detection of high-risk drinking in men (AUC: 0.82 versus 0.77; $p = 0.02$). The differences between the two tests were not significant for detection of intermediate-risk drinking in either men or women, or for detection of high-risk drinking in women.

If test performance at a single test threshold is chosen (i.e., CDT > 26 U/liter for women and >20 U/liter for men; and GGT > 40 U/liter), CDT was a more specific (particularly among men), but less sensitive, test than GGT.

All markers performed better in detection of high-risk drinking (more than 80 g/day in men; more than 40 g/day in women) than in detection of intermediate-risk drinking (>40–80 g/day in men; >20–40 g/day in women). Subjects with a diagnosis of alcohol dependence in the past year had higher marker levels than those without such a diagnosis. Age, sex, and BMI all affected marker results, but the direction of effect varied for different markers.

The results of the current study reveal that, in men, CDT, as measured by the CDTect™ kit, is a slightly better marker than GGT in detection of high-risk alcohol consumption in men, when considering the balance of sensitivity and specificity across the range of marker values. In women, CDT was not significantly better than GGT in detection of high-risk consumption. CDT shows no advantage over GGT in

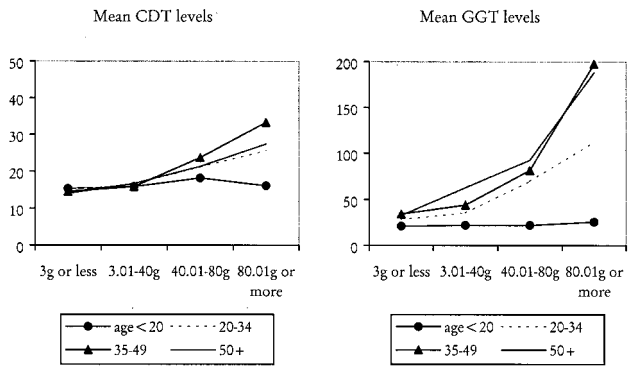

Fig. 2. Mean CDT and GGT levels according to average daily alcohol consumption in the past month by age group.

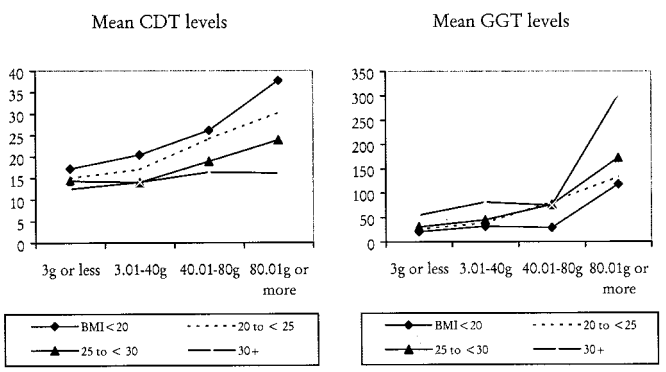

Fig. 3. Mean CDT and GGT levels according to average daily alcohol intake in the past month, by body mass index, in kg/m^2.

Table 4. Significant Predictors of CDT, GGT, and AST Levels From Multiple Regression Analyses

	CDT		GGT		AST	
	β	B (95% CI)	β	B (95% CI)	β	B (95% CI)
Sex[1]	0.14***	0.15 (0.09–0.21)	−0.17***	−0.34 (−0.44–−24)	−0.17***	−0.20 (−0.26–−0.13)
Age group	0.09***	0.03 (0.02–0.06)	0.25***	0.19 (0.15–0.22)	0.12***	0.05 (0.03–0.08)
BMI	−0.24***	−0.02 (−0.03–−0.02)	0.11***	0.02 (0.01–0.03)		
White[2]			−0.08*	−0.18 (−0.36–−0.001)		
Montreal site[3]	−0.10*	−0.11 (−0.19–−0.03)			−0.09*	−0.09 (−0.19–−0.01)
São Paulo site[3]			0.18***	0.36 (0.21–0.50)	0.11**	0.13 (0.03–0.23)
Sydney site[3]	−0.07*	−0.09 (−0.18–−0.001)				
Tobacco smoking	0.06*	0.03 (0.002–0.063)	0.06*	0.06 (0.01–0.12)		
Lifetime alcohol dependence[4]					0.07*	0.08 (0.01–0.15)
Grams alcohol consumed per day[5]	0.36***	0.11 (0.09–0.13)	0.25***	0.19 (0.16–0.22)	0.27***	0.09 (0.16–0.22)

Note: Total R for the multiple regression models were: CDT = 0.49; GGT = 0.56; AST = 0.45.

The following variables were not found to be significant predictors: Black, Asian or Indian (reference category in both cases was "other"); Sapporo site (reference category Helsinki).

* $P < .05$; ** $P < 0.01$; *** $P < 0.001$.

1. Reference category: male.
2. Reference category: other.
3. Reference category: Helsinki.
4. Reference category: no lifetime ICD-10 alcohol dependence.
5. Mean grams alcohol consumed per day in the past month.

detection of intermediate-risk consumption in men. CDT remains a significantly better test than AST in detection of intermediate- or high-risk drinking in men and high-risk drinking in women. GGT was the only marker to perform better than chance in detecting intermediate-risk consumption (>20–40 g/day) in women.

The different susceptibility of men and women to alcohol-related harm was considered in selecting the consumption categories used as reference. Epidemiologic studies have found that, for men, consumption of below 40 g/day of ethanol is not associated with increased morbidity or mortality and may be associated with some benefits to health (Baum-Baicker, 1985). Above this level, risk progressively increases (English and Holman, 1995). Alcohol intake of over 80 g/day has the potential to produce complications such as cirrhosis (Sorensen, 1989). Therefore, for men, we have used the categories of low-risk (≤40 g/day), intermediate-risk (>40–80 g/day), and high-risk drinking (>80 g/day). For women, the alcohol intake thresholds used for this analysis are half that for men, consistent with epidemiologic evidence that risk increases with consumption of 20 g/day or more (English and Holman, 1995). Accordingly, the cutoffs become 20 and 40 g/day. This imposes a much more difficult set of requirements for any biological marker, and it is not surprising that none of the markers performed well in detecting women drinking over the limit of 20 g/day. When markers were compared in detecting men or women with the same high level of alcohol consumption (60–90 g/day alcohol) the sex-related differences were no longer significant. Nonetheless, the results serve as a reminder that biological markers do not, in general, provide effective early detection of hazardous alcohol use, particularly in women. They only tend to become elevated with sustained heavy consumption.

There are a number of factors that may explain the differences in the results of the current study compared with early promising reports of CDT's performance. The current study used CDTect™, one of the commercially available kits for CDT assay. There is some evidence that this may not perform as well as other, more labor-intensive, assay methods, such as isoelectric focusing and high pressure liquid chromatography (HPLC) (Scouller et al., 2000). The early promising studies by Stibler and associates (1986) used a CDT assay method based on microanion exchange chromatography, which appears to have provided better test performance but proved inappropriate for large-scale implementation.

In addition to differences due to assay methods, some studies have used the diagnosis of alcohol dependence as their reference standard, rather than measures of hazardous or harmful alcohol consumption. The current results confirm that a diagnosis of ICD-10 dependence in the past 12 months is associated with higher marker levels, even after allowing for self-reported alcohol consumption. It is possible that alcohol-dependent persons may have underreported their drinking. Alternatively, the greater marker elevation may reflect a pattern of drinking that is more regular and sustained. Sustained heavy drinking may be associated with iron accumulation, which results in increases in the liver enzymes (Whitfield et al., 2001), although effects on CDT do not fit this hypothesis.

While the analysis did not reveal CDT to be a markedly better single test of alcohol use than GGT, there may be situations in which CDT can be used to greater advantage. CDT is likely to be more useful than GGT in patient groups with a high prevalence of liver disease or other factors known to elevate GGT levels. The current sample excluded persons with major medical conditions, such as overt liver disease, so this benefit could not have been observed. Even so, we found CDT more specific than GGT in detection of high-risk alcohol consumption in men (92% compared with 74%). However, contrary to many early reports, CDT was less sensitive than GGT (60% compared with 67%).

The reference range for GGT varies around the world.

At the chosen cutoff of 40 U/liter for both men and for women, GGT provided good specificity (90%) in its detection of high-risk drinking in women, but lower specificity in men (74%). To determine if a higher cutoff might be more useful in men, we also examined a cutoff of 50 U/liter. At this level, specificity was increased by only two percentage points to 76%, but sensitivity fell markedly from 67% to 57%. Accordingly, it was decided to retain the lower cutoff for categorical analyses.

CDT has been reported to be valuable in monitoring progress in alcohol dependence, with changes in an individual's CDT levels providing a sensitive and specific marker of change in drinking (Borg, 1996; Huseby et al., 1997a). Furthermore, the use of CDT and GGT in combination has been reported to offer benefit over either test in isolation in detection of heavy alcohol consumption (Anton and Moak, 1994; Helander et al., 1996; Huseby et al., 1997b). The finding of low correlation between CDT and GGT levels supports the role for the combined use of the two tests, though the increase in sensitivity will inevitably be accompanied by some reduction in specificity.

Factors Affecting CDT, GGT, and AST Levels

The analysis showed that CDT and GGT levels are affected by sex, age, BMI, and smoking. Obesity increased the response of plasma GGT levels to alcohol but, in the current sample, obesity had less effect on GGT levels in non- or light drinkers. This may reflect a cumulative or interactive effect of obesity and alcohol on the liver (Poikolainen and Vartiainen, 1997). Increasing BMI had the reverse effect on CDT, being associated with lower CDT levels. This confirms the effect of obesity in lowering CDT levels that has been previously reported in a sample of Australian twins (Whitfield et al., 1998). An understanding of the effects of factors other than alcohol on marker levels can help the clinician decide which is the best test to use for an individual and can assist in interpretation of results.

All three markers showed very little response to alcohol consumption in those aged less than 20. This could be due to the shorter duration of heavy drinking in young people. Alternatively, it could be related to an episodic pattern of drinking, which is more common in that age group.

We examined whether the effects of age, sex, and BMI were explained by their role in determining TBW. In theory, persons with higher TBW will have a higher volume of distribution for alcohol and, hence, a lower blood alcohol level for the same level of consumption. Correspondingly, they might be expected to have lower levels of all markers. But TBW was a predictor of CDT levels and not of GGT or AST. Furthermore, even after controlling for TBW, sex and BMI remained significant predictors of CDT levels.

The majority of studies on biochemical markers for the detection of alcohol misuse have been performed in Europe, North America, and Australia (Scouller et al., 2000). This study provided the opportunity to examine the performance of the markers in different races and cultures. Overall the biological markers showed similar performance in all centers and any racial/ethnic variation was a minor factor. It is of interest that CDT levels were found to be lower in Sapporo on bivariate analysis, but this effect did not reach statistical significance when other factors, such as BMI, were controlled. The higher liver enzyme results in São Paulo could conceivably be caused by a higher background prevalence of viral hepatitis, but this question needs further examination. While we did not have data on genetic variants in transferrin, such as transferrin D, which may be associated with altered CDT results (Helander et al., 2001), these variants are rare in Caucasian populations. The D variant is most common in African populations but our regression analyses did not reveal any association between CDT levels and race being reported as Black.

CONCLUSIONS

We have seen that the three markers studied, CDT, GGT, and AST, provide better detection of high-risk than of intermediate-risk consumption. While CDT, as measured by CDTect™, was a slightly better marker than GGT in detection of high-risk drinking in men, at standard cutoffs, CDT's high specificity was obtained at the price of only moderate sensitivity. None of the tests performed well in early detection of hazardous alcohol consumption, particularly in women. An understanding of the effect of factors such as age and BMI on marker levels is essential in ordering tests appropriately and in interpreting results.

ACKNOWLEDGMENTS

The authors thank Jack Chen for his assistance with analysis and Larry Martinez for his contribution to data interpretation. The project relied on the dedication of staff at every clinical and assay center and at the sample and data processing centers. We are indebted to the subjects who participated in the study.

The authors recognize and thank other WHO/ISBRA study group members: S. Borg, M. Dongier, H. Edenberg, C.J.P. Eriksson, M.L.O.S. Formigoni, B.F. Grant, P.L. Hoffman, K. Kiianmaa, T. Koyama, L. Legault, T-K Li, M.G. Monteiro, M. Ogata, T. Saito, M. Salaspuro, and S. Tufik.

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