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ORIGINAL ARTICLE

Abnormal Laboratory Values and Carbohydrate Deficient Transferrin

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Background: Alcohol misuse represents a substantial risk to insurance companies. The Centers for Disease Control (CDC) identifies alcohol as the second (to tobacco) most prevalent avoidable public health risk with alcoholic cirrhosis and hepatitis being the most common liver diseases seen in clinical practice.[1] Public Health reported prevalence of chronic alcohol misuse in the general population is 2.8%, (range 1.2 to 5.6%).[2] CDC surveys report that the prevalence of alcohol misuse is negatively correlated with age, education, and income. The reported prevalence of alcohol misuse in the affluent (higher than median income), older (older than 45 years), and educated population (graduated from college) is less than 2%.[3]

Elevations of serum liver enzyme, high HDL and/or smoking are positively correlated with alcohol consumption.[4-8] But these markers are non-specific indicators and are of limited usefulness in the underwriting of potential alcohol abuse. Biological markers that are increased only by alcohol can be used to resolve the ambiguity. Carbohydrate deficient transferrin, CDT, is a marker elevated by consumption of 4 to 5 alcohol-containing drinks per day. This paper reports data for the alcohol marker, CDT, in the context of insurance applicant testing.

Results: Abnormal levels of CDT were detected in 0.5% of the general insurance population. Applicants' samples with liver enzyme elevations were positive for CDT in 2.55% of cases. Gamma glutamyl peptidyl transferase (GGT) was elevated in 70% of CDT positive applicant samples. Five percent of tobacco users and 2% of applicant samples with a HDL greater than 75mg/dL tested positive for CDT. For CDT positive applicants, 60% were tobacco users.

Conclusion: In the general insurance applicant population, the prevalence of CDT confirmed alcohol abuse is low in comparison to the data reported by CDC for the general population, 0.5% compared to 2%. Reflex testing of tobacco positive applicants identifies the largest group of CDT positive samples, 5%. CDT is positive 2% and 2.5% respectively, for samples with either a high HDL or elevated liver enzyme(s). For CDT positive applicant samples, GGT is the most commonly elevated serum liver enzyme. GGT and/or AST identified 97% of CDT positive applicant samples tested due to liver enzyme elevations.

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Background

Alcohol consumption has both adverse and beneficial effects. In any population, there is a balance of effects dictated by the genetic makeup of the population and the pattern of alcohol use.[9] The old adage about life, "A little is fine but avoid excess in all things that you do," may not always be true for alcohol. For example, women have a 30% increased risk for development of breast cancer with even one drink per day compared to non-drinkers. But in the same population, the risk for development of coronary heart disease decreases with moderate use of alcohol. The net effect on mortality in a population will, therefore, be a balance between the prevalence of each disease and the pattern of alcohol use by each of these sub-populations.

Mortality related to alcohol use has been reported to increase for unintentional injuries, violence, suicide, cirrhosis, certain cancers, and hemorrhagic stroke, but decreases for coronary heart disease, and thrombotic stroke. The net risk or benefit differs by age, gender, genetic background and other environmental insults, such as smoking. In any population, the mixture of these risk factors will determine the overall mortality expectations of the group.

For medical underwriting, the picture is complicated by the lack of objective, reliable measures of alcohol misuse. The relationship between alcohol consumption and liver enzyme elevations is tenuous at best. The most commonly elevated enzyme, GGT, is elevated in less than half of patients that abuse alcohol. While even this low sensitivity may be acceptable the specificity is still lower at 10%-15%. Liver enzyme elevations are non-diagnostic in most cases. When the enzymes are extremely abnormal, the decision is very simple. However, the most frequent case is one of minor elevations in an asymptomatic applicant.

Applicant serum samples with minor liver enzyme elevations may be examined using carbohydrate deficient transferrin (CDT) to evaluate possible alcohol risk. CDT has exquisite specificity, approaching 100% in most studies. But as reported by Bird,[10] the marker has less than optimal sensitivity. Sensitivity for CDT has been reported to be 20% to 90%, depending on the study population and the prevalence of alcohol abuse in the population. The relationship between CDT and liver enzyme elevations has not been reported for a large general population model. This paper reports on the relationship between CDT and the liver enzymes for the insurance applicant population.

Method and Materials

All chemistry tests were run on a Hitachi 747 Chemistry Analyzer with Boehringer Mannheim Corporation reagents without modification. Samples for which CDT testing had been ordered were first screened with Axis %CDT TIA Assay, Axis Biochemicals ASA Oslo, Norway. Separation of transferrin with the Axis %CDT TIA procedure is by microanion exchange chromatography. The Axis %CDT TIA test is abbreviated in the text of this paper as Axis.

Samples that screened positive by the Axis test were separated with capillary zone electrophoresis (CZE), Bio-Rad Biofocus 3000, Richmond, California.[11,12] Transferrin in the sample was first isolated by immunoaffinity chromatography. Anti-transferrin antibodies were attached to a solid support. Passing the sample thorough the solid phase immunoaffinity column then isolated all the transferrin from the sample. The affinity retained, purified transferrin was then eluted from the column with glycine buffer pH 2.8. The pH of the sample is adjusted and the transferrin is saturated with iron. The isoforms of the purified transferrin were then quantitated by CZE on the Biofocus 3000.

The percent CDT was calculated by dividing the sum of disialo, monosialo, and asialotransferrin by the total transferrin and multiplying the result by 100. Samples were reported CDT positive if the CZE concentration for CDT was greater than or equal to 2.5%.

Study Populations

Six populations were studied to evaluate the relationship between the liver enzymes and the CDT test. Samples were from both clinical and insurance populations.

Group 1 - Clinical Rehabilitation Group

The sensitivity and specificity for CDT in the clinical population has previously been reported by the authors.[11,12] This population was tested by CZE only. The study group included 146 patients at Schick Shadel Hospital, a Seattle Drug and Alcohol Rehabilitation Clinic.

Group 2 - Prevalence of CDT in the Insurance Population

To determine prevalence of CDT in the insurance population, a group of 397 applicants,

selected at random, were tested with both the Axis and CZE CDT tests.

Group 3 – Comparison of Axis and CZE
The relationship between Axis positive samples and the CZE CDT confirmation assay was studied in 305 consecutive Axis positive samples.

Group 4 - Applicants with Elevated Liver Enzymes
A population of 11,477 applicants with high liver enzyme levels was tested for CDT. 87.4% of the applicants with liver enzyme elevations were male and 12.6% were female. The age of the population was 17 to 92 years (median 44).

Groups 5 and 6 - HDL and Smoking as Reflex Markers
From the clinical trial data, it was evident that liver enzymes have poor sensitivity for alcohol misuse. Consequently, two alternative surrogate markers, HDL and cotinine, were evaluated to determine the percent of applicants with these characteristics that were CDT positive. To study this possible relationship, 100 applicants with HDL concentrations of 75mg/dL or higher, and a group of 101 cotinine positive applicants were screened for CDT.

Results
Liver enzyme data for Group 1, a drug/alcohol rehabilitation population, and the general insurance applicant population are presented in Table I. The serum samples were tested as described in the methods section. The percent of applicants or patients with liver enzyme(s) levels greater than the upper limit of normal (ULN) was determined and their relative percentage calculated. From the clinical data, only 53% of people drinking more than 4 to 5 drinks per day had elevated liver enzymes.

Liver enzyme elevations are both insensitive and non-specific markers of alcohol misuse. Therefore, it is important to determine the prevalence of CDT in the insurance population without pre-selection of individuals with elevated liver enzymes. To establish the insurance population prevalence for CDT, a group of random samples (n=396) were tested with both the Axis and CZE CDT assays. For comparison, 11,477 applicants with high liver enzyme levels, tested for CDT, are included in Table II. The applicants with high liver enzymes had been selected from a population of 123,513 applicants. The percent positive in both cases were calculated for the population that the samples were selected from; i.e. the prevalence

Table I

Incidence of Liver Enzyme Elevations in the Insurance Population and Alcohol Rehabilitation Population

	Insurance Population	Drug/Alcohol In-patient Population
ALT	8.6%	30%
AST	2.9%	21%
GGT	8.3%	46%
Any Enzyme	14.5%	53%

Note: The sum of each column is less than the numerical sum due to multiple enzyme elevations of some samples.

for CDT positives in the population with high liver enzymes is 293/11,477 (2.55%).

Selection of the enzyme(s) that best detects alcohol misuse has been very confusing. GGT is often listed as the enzyme most commonly elevated by alcohol. However, GGT and the transaminases are highly non-specific indicators of liver damage, with only a small percentage actually related to alcohol misuse. In order to evaluate the relationship between the liver enzymes and CDT, the data are separated by type of enzyme. Data are presented in Table III. In increasing order of sensitivity, ALT, AST and GGT were elevated in CDT positive applicants. The most sensitive marker, GGT, was elevated in 70% of CDT positive applicants. GGT and/or AST identified 97%(285/293) of all CDT positives applicants with elevated liver enzymes. The fewest CDT positives, 2.7% (8/293), were associated with applicants with only ALT elevated. Of CDT positive applicants, 64% have liver enzyme elevations of less than 2 times the upper limit of normal (ULN).

Currently CRL and LabOne use the Axis assay to test applicants for abnormal amounts of CDT. As a part of the normal testing procedure at CRL, Axis positive samples are repeat tested by CZE. In order to investigate the relationship between the two methods, the confirmation rate for CZE was determined for 305 consecutive Axis positive samples, study Group 3. No CDT was found in 36 of those samples and no apparent reason was noted for why they had screened positive. Of the remaining 269 samples only 193/305 (63%) were confirmed positive by CZE.

Table II

Prevalence of CDT in the Insurance Population

	Total	AXIS Positive	CZE Positive
Random Applicants	396/396	3(0.75%)	2(0.5%)
High Enzyme(s)	11,477/123,513	485(4.2%)	293(2.55%)

Table III

The Degree of Liver Enzyme Elevation and The Correlation with Positive CDT

	High	1 to <1.5X	1.5 to <2.0X	2.0 to <3.0X	> 3X
ALT	102/293(35%)	47/102 (46.1%)	19/102 (18.6%)	28/102 (27.4%)	8/102 (9.8%)
AST	129/293(44%)	65/129 (50.4%)	27/129 (20.9%)	25/129 (19.4%)	12/129 (9.3%)
GGT	204/293(70%)	76/204 (37.2%)	38/204 (18.6%)	42/204 (20.6%)	48/204 (23.5%)
Total	293	143	40	54	56

Note: The column total is less than the sum of the number of abnormal samples due to some samples having multiple elevations. The samples were divided into quartiles based on multiples of the upper limit of normal (ULN).

Gender is a key demographic indicator for alcohol misuse. Data for the study populations were separated by gender. Women represent 38% of insurance applicants, but account for only 9% of CDT positive samples. These data correlate well with public health studies which report men are far more likely to misuse alcohol than are women.[1] See Table IV.

Age is a key factor in all risk behaviors including alcohol misuse. An analysis of age and CDT prevalence is presented in Table V. The data are also separated by gender. The average age for male applicants that test positive for CDT was slightly older (44.1 years) than those that test negative (43.5 years). In contrast, women that test positive (36.2 years) were 10 years younger than women that test negative (46.4 years).

Many drinkers are also smokers. To study this relationship, the prevalence of cotinine in the CDT positive population was investigated. About 20% of applicants are smokers; i.e. positive for cotinine. However, in the CDT positive population, almost 60% use tobacco, a 300% increase in prevalence. In particular, 67% of CDT positive women use tobacco compared to 16% of female insurance applicants. Likewise, 59% of CDT positive men use tobacco compared to 19% of male insurance applicants. The smoking data are presented in Table VI.

This high prevalence of cotinine positive applicants in the CDT positive population suggests that smoking status might be a good surrogate marker to identify applicants with a high probability of being CDT positive. To investigate this possibility, 101 cotinine positive samples (Group 5) were assayed for CDT. Liver enzyme elevation(s) is a possible confounder in the analysis. Therefore, the data are analyzed for liver enzyme status and CDT and

Table IV

CDT and Gender

	All Applicants	Elevated Liver Enzyme(s)	CDT Positive
Female	38%	12%	9%
Male	62%	88%	91%

Table V

CDT and Age of Applicants

	Mean Age Female	Mean Age Male
High Enzyme(s)	45.6 (24 to 92)	43.6 (16 to 74)
CDT Negative	46.4 (24 to 92)	43.5 (16 to 74)
CDT Positive	36.2 (25 to 46)	44.1 (25 to 73)

Table VI

Cotinine and CDT Prevalence.

	Cotinine Positive	Female Smoker	Male Smoker
CDT Negative	19%	16%	19%
CDT Positive	59%	67%	59%

are presented in Table VII for this group of smokers. In this random group, 5 applicants were CZE CDT positive. Of the 5 CDT positives, only 2 would have been detected due to elevated liver enzyme(s).

Serum High-density Lipoprotein (HDL) concentration is known to increase in response to alcohol intake. While this may have important implications for the reduction of coronary artery disease, do high levels of HDL correlate with excess alcohol intake? To evaluate this relationship, 646 samples with elevated liver enzymes that screened positive with the Axis test were analyzed for their HDL concentration. The samples reported, as CDT abnormal had been confirmed positive by CZE. Data are presented in Graph 1. Note that the CZE CDT positive applicants are not symmetrically distributed and their greatest prevalence is in applicants with higher HDL values.

The distribution of HDL values suggests that HDL might be an effective screen for alcohol misuse. In order to evaluate this relationship, 100 insurance samples with HDL values of 75mg/dL or higher was tested for CDT (Applicant Group 6). The data are presented in Table VIII. As in the analysis of smokers, liver enzyme elevation(s) is a confounder. Therefore, the data are also separated by liver enzyme status. In this random group, 2 applicants were CZE CDT positive. Of the 2 positives, one would have been identified due to

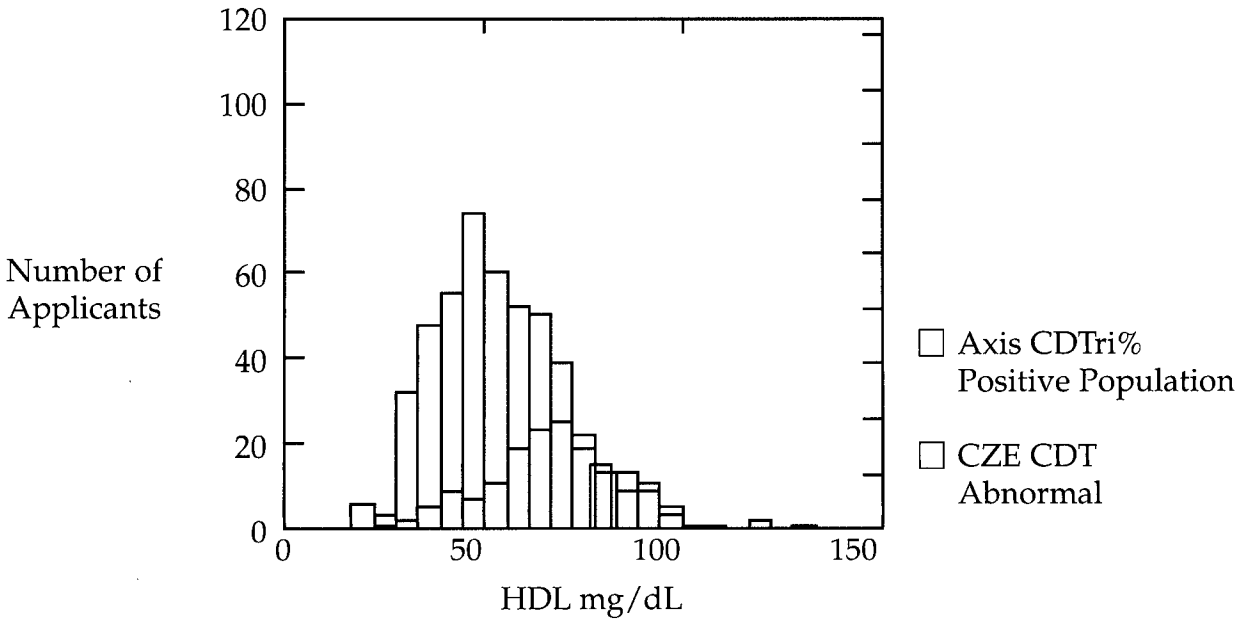
Table VII

Liver Enzyme Levels and % CDT Results in Smokers.

	Population	Liver Enzyme less than ULN	Liver Enzyme greater than ULN
CDT Negative	96	85 (84%)	11 (11%)
CDT Positive	5	3 (60%)	2 (40%)
Total	101	88	13

Graph I

Comparison of HDL and CDT data



high liver enzyme levels, while, high HDL would identify the second.

Conclusions

The prevalence of alcohol misuse has been widely studied. Public health surveys have been criticized as only educated estimates of the true prevalence due to under reporting of the surveyed population. The most recent CDC data on heavy alcohol consumption is for 1994 and 1995. The prevalence ranges from 1.2% in Oklahoma to 5.6% in Nevada (median 2.8).[3] In comparison, 2.55% of insurance applicants with liver enzyme levels greater than the upper limit of normal are positive for CDT. See Table III. Two possible explanations are 1) the insurance prevalence for alcohol misuse is lower than the general population; or 2) the CDT assay is insensitive.

The prevalence of chronic alcohol misuse in the insurance buying population was initially estimated as 6% to 10% based on CDC prevalence surveys. Early insurance laboratory reported prevalence ranged from 4% to 25% for applicants with liver enzyme elevation(s). With the introduction of each new CDT screening assay, the reported prevalence of CDT positive applicants has decreased to the 4% range. When general insurance applicant population statistics are prepared, the prevalence is 0.5% to 0.75%. Population based statistics are obtained by testing a random group of applicants without the bias introduced by selecting applicants using surrogate markers, i.e.: high liver enzymes concentration, smoking or high HDL concentration. Population based statistics may, in fact, over estimate the prevalence due to possible false positives in a low prevalence population. But the question still remains, is 0.5% to 0.75% a reasonable estimate of the true prevalence for alcohol misuse in insurance applicants?

The most recent public health survey of alcohol use that separates population data by gender, income, education, and age was reported in 1994.[3] The prevalence of alcohol misuse, defined as five or more drinks in a single drinking episode, varies from a low of 0.7% for women, to 1.8% for college graduates, to 2.5% for people above the median income, to 11% for people 18 to 29 years of age. The prevalence of alcohol misuse is highest among low income, young males with less than a high school education.

Population demographic differences may in part explain the differences in CDT prevalence reported by different insurance testing laboratories. Most of CRL clients write policies in the older more affluent market where the prevalence for alcohol misuse is statistically lower than for other population mixtures. Another reason for the discrepancy in inter-laboratory prevalence is differences in testing methodolo-

Table VIII

Liver Enzyme and CDT Results in Applicants with High HDL.

	Population	Liver Enzyme less than ULN	Liver Enzyme greater than ULN
CDT Negative	98	85 (85%)	13 (13%)
CDT Positive	2	1 (50%)	1 (50%)
Total	100	86	14

Both CDT positive samples had HDL of 90mg% or greater. Reflex testing for high HDL concentrations identified only one additional positive per 100 HDL elevated applicants.
ULN = upper limit of normal.

gy. A recent article in Clinical Chemistry reported that 50% of samples reported as positive using IEFF/WB/LD are negative when separated by HPLC, Bean et al.[13] The same authors report a specificity of 75% for samples separated by Axis. Only when the samples were confirmed by HPLC does the specificity reach 100%. Other laboratories have suggested that the Axis is now the "gold standard of CDT testing".[14] The Axis test requires confirmation testing by HPLC,[6] therefore it cannot be a gold standard test. In our hands, HPLC and CZE give the same result for identification of both normal and abnormal concentrations of CDT (data not shown).

Is CDT testing insensitive to alcohol misuse in the insurance population?[10-12] The reported sensitivity for CDT testing is only 20% to 45% in binge or regular users of 10-70 grams of alcohol per day. In comparison, people that chronically consume 80 grams or more of alcohol per day were positive for CDT 60% to 88% of the time. In comparison to other available markers, the CDT test is the most sensitive and specific indirect test currently available to detect alcohol misuse.

Why are so few samples with liver enzyme elevation(s) confirmed positive by CDT testing? First, the prevalence of chronic alcohol abuse is lower in the insurance buying population than the general population. Second, in the past decade the percentage of samples that test positive for GGT and or ALT elevation(s) has doubled, going from 4% to over 8%, for each. During this same period, per capita alcohol consumption has decreased by 20%. During the past three years, people that report consuming 60 or more drinks during the previous month had been stable at about 2.8% (2.8 to 3.0).[2] Therefore, the increased prevalence of liver enzyme elevations cannot be attributed to alcohol consumption, which actually has decreased. One reason for the observed increase in prevalence of liver enzyme elevations is the rise in use of non-steroidal anti-inflammatory drugs. Use of these medications has more than doubled during this same period. In addition, 30% of the population is currently considered to be obese. More than half of liver enzyme elevations can be attributed to these two causes.

The most effective algorithm for identifying all CDT positive applicants is by uniform testing of the whole population. But, one word of caution...in a low prevalence population, the number of false positives would be high if only the Axis -screening assay is used. Currently, 50% of Axis positive samples are confirmed positive by CZE. This percentage is for all samples submitted to confirmation testing by CZE in the past 12 months. Therefore, for samples that screen positive, there is a 50% chance that they are in fact negative. Bean *et al* recently reported that 25 % of Axis positive samples and 50% of IEF/IB/LD positive samples are negative by HPLC.[13] The benefit of universal screening is to identify the maximum number of applicants who abuse alcohol. But, if the Axis test is used to screen the population, all positives should be evaluated with HPLC or CZE. No test has proven effective in the identification of all applicants that misuse alcohol, but CDT is the most sensitive and specific marker available.

The best enzyme marker for alcohol misuse is GGT. In the applicant with elevations of GGT and/or AST, the best reflex test would be CDT. The combination of these two markers identified 97% of CDT positive applicant samples with elevated liver enzymes. The high correlation between GGT and CDT also reflects a preselection bias. Most insurance clients reflex CDT from a high GGT, fewer reflex CDT from high ALT and AST concentrations. For samples with only a high GGT, if the CDT is negative, additional reflex testing for Hepatitis C will most often be negative.[15] The circumstance is different if ALT is elevated. Samples with ALT elevation, whether alone or in combination with the other enzymes, should be tested for Hepatitis C antibodies. A combination of CDT and viral hepatitis tests should identify the two most prevalent pathological causes of liver disease.

In the selection of non-liver surrogate markers, both high HDL and/or smoking status will increase the number of CDT positive applicants found. The addition of HDL with concentrations greater than 75mg/dL as a surrogate is projected to increase the number of CDT positives by 6%. That is based on CDT testing of 450 additional samples per 10,000 applicants. Those additional tests are expected to find 4.5 more CDT positive applicants. Currently 14% of samples have liver enzyme elevations. The addition of HDL as a reflex marker would increase the number tested for CDT to 18.5%, an increase of 32%. Therefore, testing of applicants with HDL values of 75mg% or higher will increase the cost of CDT testing by 32% while identifying an additional 6% that are CDT positive.

In comparison, the use of cotinine as a surrogate marker would double the cost of CDT testing. This is based on a smoker's prevalence of 20%. 14% of smokers would be positive for liver enzymes and, therefore, the net would be approximately 16%. The combination of the two reflex criteria would result in 30% of samples being tested for CDT. Reflex testing from smoking status is projected to double the number of CDT positives. That projection is based on 1,700 samples tested per 10,000 applicants with 51 additional positives identified. In this regard, tobacco use would be a more effective reflex marker than HDL.

One additional marker is worth review. Serum or whole blood alcohol is an inexpensive and obviously direct marker for consumption. Alcohol testing may be extremely useful in the rehabilitated population where any alcohol is an ominous sign. It is also useful in applicants with a positive Motor Vehicle Report(s) (MVR) or criticism in an Attending Physician Statement (APS). Due to a high prevalence of alcohol abuse in those populations, CDT would have its highest positive predictive value. The combination of CDT and blood alcohol allows for the effective identification of drinkers.

Through the careful selection of reflex markers, it is possible to reduce the alcohol risk in new business while minimizing the cost of reflex testing. The CDT test identifies applicants who misuse alcohol, but it is not 100% sensitive. CDT positive applicants should be subject to more intensive underwriting. Only when CDT results are used with good judgment in the context of all available underwriting information, can excess risk due to alcohol misuse be minimized in the insurance buying population.

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