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## Use of contemporary biomarkers in the detection of chronic alcohol use

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### Summary

Alcohol is the most commonly abused substance yet alcoholism is frequently undiagnosed. The misuse of alcohol is common and frequently an occult problem. More than 10% of current drinkers meet diagnostic criteria for alcohol abuse or dependence while the lifetime prevalence for these conditions in outpatient settings ranges from 16 to 36 percent. Long-term, heavy drinking is associated with significant morbidity, mortality, and economic costs. Clues to alcohol use can be discovered from a patient's history and physical stigmata. Validated screening instruments such as the Alcohol Use Disorders Identification Test (AUDIT), CAGE Questionnaire, and Brief Michigan Alcoholism Screening Tests help confirm the clinical suspicion of alcohol dependence. Laboratory abnormalities of mean corpuscular volume, gamma-glutamyl transferase, alkaline phosphatase, or alanine amino transferase levels are non-specific indicators of possible alcohol-induced liver impairment. Newer, less well-known FDA-approved biochemical markers such as the Carbohydrate Deficient Transferrin and the Early Detection of Alcohol Consumption test may also be used to detect heavy alcohol abuse and to monitor relapse episodes. Brief interventions are successful, making identification and diagnosis a vital role for the family physician. Improved awareness of alcohol misuse, increased use of screening tools, and the appropriate use of biochemical markers will facilitate early intervention and successful management of patients with alcohol use disorders.

**key words:** alcohol abuse • biomarkers • contemporary diagnosis

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## BACKGROUND

The ability to recognize and detect alcohol misuse is a key skill to reduce the public impact of excessive alcohol use. Males and females of all age groups should be considered at risk from binge drinking (5 or more drinks on an occasion) to chronic alcohol abuse and dependency; however, the majority of patients are not commonly screened to diagnose problem drinking or alcoholism. This practice results in many cases of occult alcohol misuse and abuse not being detected nor diagnosed.

The more frequent use of screening tests combined with the use of new biochemical markers in patients who are suspected of alcohol abuse will improve detection and permit intervention earlier in the course of the illness. Some of these biochemical markers are currently being used to detect unsuspected alcohol use in life insurance applicants and assign them to different levels of risk. Primary care physicians should be more alert to the signs and symptoms of alcohol misuse, utilize screening instruments more frequently, use biochemical markers when indicated, and initiate treatment for alcohol use disorders more consistently in their patients. This article will provide the clinician with updated information on the use of biochemical markers to detect sustained and harmful alcohol use.

In 1998, the overall economic cost of alcohol abuse<sup>1</sup> in the U.S. was estimated at 185 billion dollars [1]. In primary care, the prevalence of lifetime alcohol dependence<sup>2</sup> ranges from 2 to 8% and the prevalence for current or lifetime diagnosis of alcohol abuse ranges from 9 to 36%, making it one of the most common psychiatric diagnosis in the general population [2]. Indeed, the lifetime prevalence of alcohol abuse and alcohol dependency was the highest of any of the 44 adult disorders sampled by the Epidemiological Catchment Area Survey [3]. Alcohol dependence, the most severe form of alcoholism, results in over 100,000 deaths annually [4].

Those who misuse alcohol have higher morbidity caused by domestic violence, injuries, assaults and homicides [6,7]. Motor vehicle and boating accidents also occur more commonly in those who are impaired by alcohol. Alcohol use is associated with 49% of all fatal automotive crashes [8]. Seventeen to 53% of falls that present in ERs are alcohol related and blood alcohol levels indicate intoxication in 40–64% of people dying in fires [9].

Many signs and symptoms of alcohol use exist in addition to clues in the patient's family or medical history. Co-morbid conditions in men include drug abuse and antisocial personality disorder and in women anxiety and mood disorders [10]. Alcoholics are seven times (70%) more likely than the general population (10%) to

smoke more than 20 cigarettes per day [11]. Alcohol use is associated with 13% of breast cancers, 74% of cirrhosis and 72% of chronic pancreatitis [12]. In addition, physical manifestations of chronic alcohol use can be discovered on physical exam (Table 1). The challenge for the clinician is to detect alcohol use at an early stage.

## SCREENING FOR PROBLEM DRINKING, ALCOHOL USE AND DEPENDENCE

Several validated screening instruments can be self-administered (by patients) to identify problem drinking. A widely used instrument is the Alcohol Use Disorders Identification Test (AUDIT) [13]. The National Institute on Alcohol Abuse and Alcoholism designed a shorter screening instrument, The Quantity/Frequency Questionnaire. If either of these instruments suggests problem drinking, further evaluation of the patients is warranted. To detect alcohol use and dependence a CAGE questionnaire is recommended [14]. The Brief Michigan Alcoholism Screening Test (BMAST) and the Tolerance, Worry, Eye Opener, Amnesia, and Kutdown (TWEAK) are 10 and 5 question tests, respectively, that detect alcohol use disorders based on the response by patient contacts such as spouse and friends. A more detailed review of these tests was recently published [15].

## NON-SPECIFIC BIOCHEMICAL MARKERS

Acute or recent use of alcohol can be detected by blood alcohol levels or breath analysis in the acute care setting. Routine laboratory data may contain clues helpful in increasing suspicion of selected patients who may need further assessment, yet these tests are either non-specific or lack sensitivity for detecting severe chronic alcohol use [16]. Elevations in mean corpuscular volume (MCV) and aspartate aminotransferase (AST or SGOT) are classically related to alcohol abuse even though they are non-specific. Some clinicians also use gamma glutamyl transferase/transpeptidase (GGT/GGTP) to support the diagnosis of heavy drinking but this biomarker can be elevated by some antiepileptic medications, obesity or as a result of chronic viral hepatitis [17].

## NEW BIOMARKERS OF SUSTAINED & HARMFUL ALCOHOL CONSUMPTION

### Carbohydrate-Deficient Transferrin (CDT)

Heavy ethanol consumption, defined as more than 60 g of ethanol (5 beers, 4 glasses of wine or 3 mixed drinks) per day for 7–10 consecutive days, causes hepatocytes to produce molecules of transferrin that are deficient carbohydrates [18]. Hence the term Carbohydrate-Deficient Transferrin. The mechanism by which chronic

<sup>1</sup> Alcohol abuse is defined by at least one of the following events occurring during the course of one year: Recurrent use resulting in failure to fulfill major role obligations, recurrent use in hazardous situations, recurrent alcohol-related legal problems, and, continued use despite social or interpersonal problems caused or exacerbated by alcohol [5].

<sup>2</sup> Alcohol dependence is defined by at least three of the following events in one year: 1) Tolerance, which is the need for increased amounts to achieve effect or diminished effects from same amount; 2) withdrawal; 3) a great deal of time spent obtaining alcohol, using it, or recovering from its effects; 4) important activities given up or reduced because of alcohol; 5) drinking more or longer than intended; 6) persistent desire or unsuccessful efforts to cut down or control alcohol use; and, 7) continued use despite knowledge of a physiologic problem caused or exacerbated by alcohol [5].

**Table 1.** Common alcohol-related medical disorders.

| System                    | Disorder  |                              |
|---------------------------|---|------------------------------|
| Central nervous system    | Acute delirium/intoxication                                       | Delusions                    |
|                           | Hepatic encephalopathy  | Tremor                       |
|                           | Wernicke-Korsakoff Syndrome                                       | Agitation                    |
|                           | Cerebrovascular accidents   | Emotional Lability           |
|                           | Cerebral atrophy  | Wide-based gait              |
|                           | Cerebellar degeneration   | Syncope                      |
|                           |   | Memory loss                  |
|                           | Depression  | Anxiety                      |
| Peripheral nervous system | Neuropathy  |                              |
| Muscle-skeletal system    | Myopathy  | Osteopenia                   |
|                           | Hyperuricemia   | Palmar erythema              |
| Gastrointestinal          | Fatty liver   | Esophagitis                  |
|                           | Hepatitis   | Gastritis                    |
|                           | Cirrhosis   | Pancreatitis (acute/chronic) |
|                           | Hepatoma  | Jaundice                     |
|                           | Ascites   | Varices                      |
|                           |   | Tachycardia                  |
| Cardiovascular System     | Hypertension  |                              |
|                           | Cardiomyopathy  |                              |
|                           | Atrial or Ventricular arrhythmias                                 |                              |
|                           | Hyperlipidemia  |                              |
| Hematopoietic             | Anemia  |                              |
|                           | Coagulation abnormalities   |                              |
|                           | Leukopenia  |                              |
|                           | Thrombocytopenia  |                              |
|                           | Macrocytosis  |                              |
| Genitourinary system      | Testicular atrophy  |                              |
|                           | Erectile dysfunction  |                              |
|                           | Amenorrhea  |                              |
| Dermatologic              | Facial telangiectases   |                              |
|                           | Bruising  |                              |
|                           | Spider angiomas   |                              |
|                           | Palmar erythema   |                              |
|                           | Superficial infections  |                              |
|                           | Rosacea   |                              |
|                           | Seborrheic dermatitis   |                              |
|                           |   |                              |
| Electrolyte abnormalities | Deficiencies of: Potassium, Magnesium, Zinc, Calcium, Phosphorous |                              |
| Nutritional abnormalities | Deficiencies of: Folate, Thiamine, Pyridoxine, Niacin, Riboflavin |                              |
| Miscellaneous             | Fetal alcohol syndrome  |                              |
|                           | Hypoglycemia  |                              |
|                           | Ketoacidosis  |                              |
|                           | Hypomagnesia  |                              |
|                           | Hypophosphatemia  |                              |
|                           | Elevated hypothyroidism   |                              |

ethanol consumption causes an elevation of CDT concentrations in serum is still not understood. Increases in CDT may represent the effects of both increased trimming of carbohydrates in serum and/or abnormal synthesis of carbohydrates in the hepatocyte [19].

In 2001, the Food and Drug Administration approved the %CDT turbidimetric immunoassay (% CDT TIA, Axis Shield, ASA, Norway) test as a marker for sustained and harmful alcohol use [20]. The CDT is similar to the hemoglobin A<sub>1c</sub> value for diabetics in that it provides both quantitative and qualitative information about alcohol intake over the past two weeks, not 3 months as

with the A<sub>1c</sub> values. If a screening instrument, physical exam or behavior suggests alcohol misuse CDT can be used to confirm or support a diagnosis of chronic alcohol abuse. It can also be used to monitor abstinence and detect relapses in patients undergoing treatment.

The %CDT TIA separates and measures CDT as well as total transferrin present in the same serum sample. Thus, CDT is measured as a ratio of total transferrin. The main technological advantage of the %CDT TIA is its availability in an array of cost-effective, automated formats. Turbidimetry can be measured manually in a microtiter plate reader or by several instruments: Berhing, Cobas,

**Table 2.** Comparison of biochemical markers of chronic heavy alcohol use.

| Test          | CDT   | EDAC – screen   | GGT   |
|---------------|---|---|---|
| Use           | Detects sustained and harmful alcohol use<br>Monitoring therapy – It reverses in 14–21 days | Detects binges, at-risk drinking and chronic alcohol consumption                                  | Quantity and frequency alcohol use over past month              |
| Advantages    | High specificity<br>Heralds relapse episodes  | Elevated prior to liver damage<br>Uses routine lab data   | Elevated prior to liver damage<br>Easy to perform, routine test |
| Identifiers→  | Optimal performance in adult Caucasian males  | Good sensitivity in the young and in females  |   |
| Disadvantages | Low sensitivity in the young  | Remains elevated 2–3 months after cessation of drinking   | Non-specific  |
| Data*         |   |   |   |
| Specificity   | 82–100%   | 79–97%  | 11–85%  |
| Sensitivity   | 44–94% (gender effect)  | 61–94%  | 34–85%  |
| FDA Approved  | Yes – CPT code 82373<br>(reimbursement rate = \$25.23)                                      | Has a waiver – no CPT code  | Yes – CPT code 82977<br>(reimbursement rate = \$9.95)           |
| Cost          | \$30 per test   | \$25 for test panel<br>\$5 for EDAC   | Less than \$10  |
| Challenges    | False positive with:<br>Severe liver disease<br>CDGS<br>Genetic variants of transferrin     | Ongoing research is evaluating the effects of non-alcohol related liver diseases on the EDAC test | Elevated in many situations unrelated to alcohol abuse          |

\* Data represents range for heavy drinkers from all the references cited in this review

Hitachi and Kone Optima. The two distributors of the % CDT kit in the U.S. are Bio-Rad (Hercules, CA) and Equal Diagnostics (Exton, PA). The current cost to health care providers for the %CDT TIA averages \$30 per test and is reimbursed when clinically indicated.

The main difference between CDT and the previous, more traditional markers of alcohol abuse is diagnostic accuracy (Table 2). Indeed, CDT's major asset is its high specificity. This means that a CDT positive result is almost always indicative of sustained heavy drinking. For instance, CDT is not affected by any of the following diseases or their treatment; hypertension, asthma/bronchitis, angina pectoris, diabetes mellitus, adipositis/lipid metabolism disorder, depression, and disorders of the digestive tract [21]. Indeed, there are only a few non alcohol-related conditions that will render false-positive CDT tests: the rare genetic D variants of transferrin, the carbohydrate-deficient glycoprotein syndromes (CDGS) that affect mainly newborns and severe chronic viral hepatitis [22].

The sensitivity of the CDT test (its ability to detect harmful alcohol consumption) depends on several parameters such as amount of alcohol ingested, extent of drinking behavior, time of sample collection after cessation of drinking, age and gender [23–25]. Even though a wide range of sensitivities (22–81%) is reported in various populations, CDT is most sensitive in middle-age Caucasian males [26]. In some instances, CDT has shown less sensitivity in females [27]. The main potential explanation for this finding relates to variation in hormonal status such as the use of contraceptives, hormone replacement therapy and pregnancy [28,29]. Currently, the best option to detect harmful alcohol

consumption in females is to use a combination of different tests such as CDT and GGT [30], CDT, GGT and MCV [31] or the Early Detection of Alcohol Consumption (EDAC test) [32].

### The Early Detection of Alcohol Consumption (EDAC) Test

The EDAC is a method of interpreting routine blood profiles to identify individuals who routinely consume large volumes of alcohol. This drinking can be either binge drinking or a more steady daily consumption of four drinks daily for men and three drinks daily for women [33]. It is important to stress that the EDAC is a method for determining heavy alcohol consumption and not alcoholism. Heavy alcohol consumption is a risk factor for the development of more serious drinking problems as well as trauma and other health and social problems. In those settings where the identification of heavy alcohol consumption may result in negative social or legal consequences, it is recommended to confirm the EDAC result with the CDT test [34]. Thus, the EDAC is more of a screening tool than CDT.

The method used to calculate the EDAC is called linear discriminant function analysis; it is a statistical model of predictions. The statistical modeling of the blood panel constituents can be thought of a 'mathematical fingerprint'. This 'fingerprint' is a representation of how closely the pattern of blood panel constituents obtained from any given patient resembles the 'idealized fingerprints' obtained previously from a well-characterized database of heavy drinkers and light/nondrinkers [32–34]. The main components used to calculate the

EDAC are monocytes, high-density lipoprotein, liver enzymes (GGT, AST, ALT) and bilirubin ratio.

The EDAC is reported with several pieces of information including the probability that the individual's profile is that of a heavy drinker, the probability that the individual's profile is that of a light drinker and the risk that the individual may develop alcohol related consequences such as alcoholism and trauma. The Probability that an individual's profile is that of a heavy drinker or P-Positive, is the degree to which the blood profile of the individual being evaluated resembles that of other heavy drinkers. Generally the higher the individuals' P-Positive value, the greater the risk of alcohol related complications.

The EDAC is available in two formats; the EDAC screen and the EDAC test. **The EDAC Screen** is the EDAC procedure conducted within a high sensitivity setting. This setting allows for the identification of most heavy drinkers but creates some loss of specificity and, as a practical matter, reduces the positive predictive value of the test. It is recommended that the EDAC screen be utilized in conjunction with the CDT test to confirm a positive results in particularly high-risk situations. **The EDAC Test** is the EDAC procedure conducted within a high specificity setting. This setting will fail to identify some heavy drinkers who would have been identified by the EDAC screen. This decreases the sensitivity while increasing the specificity and positive predictive value of the prediction. The current cost to health care providers averages \$25 for the routine test panel and \$5 for the EDAC test; the EDAC has received an FDA waiver since it is based on currently approved test.

### CLINICAL BENEFITS OF NEW BIOMARKERS

The basic relevant performance parameters of laboratory tests are sensitivity, specificity and predictive values. The clinician wants to know: 'If the patient has a positive test, how likely is he/she to have the disease?' and 'If the patient has a negative test, how likely is he/she not to have the disease?' The answer relies in the positive predictive value (PPV) and the negative predictive value (NPV) of the laboratory tests.

PPV and NPV depend not only on sensitivity and specificity but also on the prevalence of the disease. For example, as mentioned previously, the prevalence of alcohol dependence is 8–14% in the United States [15]. If we assume a prevalence rate for alcohol dependence of 10%, using any biomarker with average performance parameters of 65% sensitivity and 95% specificity rates will render a positive predictive value of 0.59. This means that there is a 59% probability that the positive result derives from an individual that abuses alcohol and a 41% chance of a false-positive result; basically similar to a coin flip. At this low prevalence, the positive predictive value of the test is inadequate for its use as a screening tool. However, a common way of maximizing the diagnostic accuracy of any laboratory test is by increasing disease prevalence. For instance, the prevalence of heavy among individuals that smoke is much greater than the prevalence of drinking in the general population. If we assume that the prevalence of alco-

hol dependence increases to 25% in smokers then the PPV of the test increases from 0.59 to 0.75. Thus, in clinical terms, the use of a screening questionnaire, historical information or a physical exam that suggests heavy alcohol use will increase the likelihood of a true positive being discovered by increasing the prevalence of the condition and therefore the accuracy of the test.

Frequently, laboratory tests with a higher sensitivity are used as screening tests and abnormal results are then confirmed with a highly specific test. Based on this general assumption and the diagnostic performances described above, the EDAC test is a good option for a screening test due to high sensitivity rates. Abnormal EDAC test results could then be confirmed with the more specific CDT test [35]. The CDT test may also be used as a confirmatory test for an abnormal HDL cholesterol result [36].

A new promising approach to diagnose alcohol abuse is the use of combinations of biomarkers to increase the sensitivity rates. Due to the limited sensitivity of any single laboratory marker, the combined measurement of the traditional MCV or liver enzyme tests with the new alcohol markers such as CDT and EDAC may enhance the ability to correctly assess alcohol abuse. Recent studies indicate that combined measurements of CDT and GGT, CDT and MCV or CDT and High Density Lipoprotein (HDL) result in improved diagnostic accuracy [36–38]. A related study shows that combining the CDT with the EDAC screen results in a sensitivity of 97.5% and a specificity of 100% for detection of alcohol abuse in individuals recruited from detoxification centers, churches and 12-step recovery programs in the Midwest [34].

CDT is useful to detect sustained rather than acute or binge alcohol use, the latter is better detected by the EDAC test or blood/urine alcohol level. CDT is a good test to monitor abstinence and relapses because cessation of alcohol consumption restores the capacity of the liver to produce normal transferrin within two to three weeks [39–41]. Therefore, a change in CDT over time can be used as an outcome measure in alcoholism treatment since the % CDT level changes differentially with drinking status [37,42,43]. Patients who relapse to heavy drinking have an average 30% increase in CDT levels when relapse is defined as having five or more standard drinks on two consecutive days [43]. The EDAC test is also a good test to monitor relapses because the panel of routine laboratory tests responds quickly to increases in alcohol consumption [44]. When monitoring abstinence, the EDAC takes longer to normalize than the CDT test.

### SUMMARY

The importance of early detection of heavy drinking in high-risk patients is amplified because brief interventions have proven successful. The use of brief screening instruments should be employed more frequently in clinical practice given the prevalence, morbidity and mortality associated with alcohol use. However, screening instruments are limited by their reliance on a patient's ability to read, degree of appreciation of their problem, and a willingness to disclose sensitive informa-

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tion. If a clinical suspicion of excessive alcohol use is present or screening instruments identify problem drinking or dependence, the use of biomarkers is a beneficial approach to detect sustained, harmful drinking.

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