Biochemical detection and monitoring of alcohol abuse and abstinence

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SUMMARY. The merits and limitations of traditional and new markers for alcohol abuse (and abstinence) are critically examined for detection and monitoring of alcoholics, hazardous drinkers and binge drinkers. The traditional markers discussed include γ-glutamyltransferase (GGT), aspartate and alanine aminotransaminases (AST, ALT) and mean corpuscular volume (MCV); new markers include mitochondrial AST, carbohydrate-deficient transferrin (CDT), serum/urine 5-hydroxytryptophol, β-hexosaminidase and acetaldehyde adducts. The strengths and weaknesses of several of the self-reporting screening questionnaires are also explored. No laboratory test is reliable enough on its own to support a diagnosis of alcoholism. Sensitivities and specificities vary considerably and depend on the population concerned. GGT continues to remain the test that combines greatest convenience and sensitivity; its diagnostic accuracy can be enhanced by combination with other traditional markers (AST, ALT, MCV). None of the newer markers offers significant advantage, although CDT seems to be better at monitoring patients for increased alcohol consumption or progress towards abstinence.

INTRODUCTION

Alcoholism represents a serious health issue with major socio-economic consequences. Physicians are likely to identify only 20–50% of patients with alcoholism who are attending for medical care.[1,2] The diagnosis is often based on the patient's self-reporting of alcohol consumption, which is notoriously unreliable[3,4] and requires a high degree of clinical suspicion. The physician may fail to appreciate the significance of many of the clinical symptoms and findings, which frequently mimic other diseases. Many heavy drinkers are in good health, with no apparent ill-effects from their excessive drinking, and are unlikely to seek medical advice;[5] they can skilfully hide their addiction and, when medical advice is finally sought, it is often too late to reverse either the organ damage or the dependence on alcohol. However, if alcohol problems are recognized at an early stage, a physician may be able to prevent their further development and progression.[6–8]

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Recommended safe limits and definitions

The safe limits for alcohol intake are controversial, as there is a wide variation in individual susceptibility to damage. Guidelines drawn up by the Royal College of Physicians advise a weekly limit of 21 units (168 g) of alcohol for men and 14 units (112 g) for women;[9] these limits have also been endorsed by the Royal Colleges of Psychiatrists and General Practitioners. One unit of alcohol contains 8 g of absolute alcohol. A can of beer or lager (450 mL) contains about 1·5 units of alcohol, a bottle of wine (750 mL) 7–10 units and a bottle of spirits around 30 units.

In 1996, 27% of men and 14% of women in Britain were consistently drinking more than these recommended limits, potentially putting their health at risk ('hazardous drinking').[10] In the age group 16–24 years, 35% of men and 22% of women exceed these amounts.[11] Although alcohol abuse can affect any individual in society, personal risk factors include a family history of alcoholism, certain occupations (e.g. publicans, business men who have long absences from family and friends), being a single man and stress.[11,12]

Definitions of different kinds of drinkers are as follows:

- *Social drinkers* usually drink not more than 2–3 units of alcohol per day and do not become intoxicated. They are unlikely to harm themselves or others through drinking. Alcohol consumption at these levels reduces the risk of developing coronary heart disease by up to 40%.[13,14]
- *Heavy drinkers* regularly drink more than 6 units a day, but without apparent immediate harm.
- *Problem drinkers* experience physical, psychological, social, family, occupational, financial or legal problems attributable to drinking (but without evidence of alcohol dependence). Consumption of alcohol generally exceeds the recommended safe limits, but may not necessarily be regular. Harmful levels of consumption are > 50 units (400 g) of alcohol per week for men and 35 units (280 g) for women. Estimates suggest that approximately 6% of men and 2% of women exceed these levels.[11]
- *Alcohol dependence*: people with a compulsion to drink, who take roughly the same amount each day, have increased tolerance in the early stages and reduced tolerance later, suffer withdrawal states if alcohol is reduced or stopped and in whom drinking takes precedence over other activities (pleasures/interests). They persist in using alcohol despite clear evidence of harm. It is difficult to estimate the true number of dependent drinkers in Britain, but recent figures suggest 7·5% of men and 2·1% of women aged 16–64 years.[15]

CLINICAL FEATURES OF ACUTE ALCOHOLIC INTOXICATION

The behavioural and clinical features of acute alcoholic intoxication are summarized in Table 1. Blood alcohol levels necessary to produce intoxication depend on a number of factors, including the rate of intake (a rapid rise in blood alcohol concentration produces greater effects than a gradual increase), the degree of individual tolerance (which is increased by previous regular alcohol consumption) and whether the individual is drinking in company or in isolation.

PHYSICAL HEALTH HAZARDS ASSOCIATED WITH ALCOHOL ABUSE

The physical health hazards and diseases associated with excessive alcohol consumption are well known (Table 2). Regular consumption of 7·5 units (60 g) of alcohol per day in men and 5 units (40 g) per day in women is associated with increasing risk of any of these diseases. Alcohol abuse can also lead to psychiatric, psychological and social problems and in pregnancy is associated with fetal alcohol syndrome; the Royal College of Obstetricians and Gynaecologists has issued guidelines on this condition (see www.rcog.org.uk/guidelines/alcohol.html; July 2001).

DETECTION OF EXCESSIVE ALCOHOL INTAKE

No exact symptom or clinical finding identifies alcohol abuse in its early stages. Le Go, a French physician, has described subtle physical signs of problem drinking and grouped them in a 'Le Go grid'.[16,17] The cardinal signs are abnormal skin vascularization (particularly facial telangiectasia), conjunctival injection, coating of the tongue, tremor of the mouth, tongue and hands. The subsequent work of Skinner *et al.*[18] concluded that clinical signs (Le Go grid, tandem gait, deep knee bend, oedema of soft palate, bruises, abrasions, cigarette burns and trauma-related scars) distinguished a group of

TABLE 1. *Clinical features and effects of various alcohol concentrations*

Blood alcohol concentration (mg/100 mL)	Clinical effects
20	Euphoria
30	Increased likelihood of having an accident
40	Disinhibited
80	Impaired coordination, legal limit for driving in UK
150	Loss of self-control, slurred speech, drowsiness, amnesia
300	Stupor, coma
500	Coma, death possible
600	Death certain

Adapted from Refs 9 and 158.

TABLE 2. *Disorders and diseases associated with excessive alcohol intake*

Organ or system	Disease or disorder
Liver	Fatty infiltration, alcoholic hepatitis, cirrhosis, liver failure
Gastrointestinal	Oesophagitis, gastritis, Mallory–Weiss tear, haematemesis, peptic ulceration, oesophageal cancer, pancreatitis, diabetes mellitus, diarrhoea, impaired absorption, weight loss, malnutrition
Nervous	Acute intoxication, 'black-outs', epilepsy, tremor (delirium tremens), dementia, Wernicke's encephalopathy, Korsakoff's psychosis, strokes, subdural haematoma (head injury), subarachnoid haemorrhage, hallucinations, peripheral neuropathy
Cardiovascular	Hypertension, arrhythmia, heart failure
Respiratory	Tuberculosis, fractured ribs, pneumonia
Lipids	Hypertriglyceridaemia
Gonads/reproduction	Men: erectile dysfunction, loss of libido, impaired spermatic function (sub- or infertility), small testes, loss of sexual hair
	Women: menstrual irregularities, subfertility, sexual problems, loss of secondary sexual characteristics
Endocrine	Pseudo-Cushing's, hypoglycaemia
Fetus	Fetal alcohol syndrome

excessive drinkers from social drinkers better than either clinical history or laboratory markers. In contrast, a World Health Organization (WHO) collaborative study found that clinical findings were generally poor as early indicators of alcohol-related harm.[19]

Various self-reporting screening questionnaires and laboratory tests ('markers') are now available to assist in the diagnosis of alcoholism. This review briefly describes the strengths and weaknesses of several of the questionnaires that are currently used in screening for excessive drinking and reports on both the conventional and new biochemical markers.

Questionnaires

The ideal questionnaire should be easy to administer, short and accurate, and correlate with other more complex diagnostic procedures and tests. Questionnaires are ideally suited for population screening and can identify up to 80% of alcoholics, but they rely on the patient's truthfulness and memory and are highly susceptible to deliberate concealment. The best known are CAGE, MAST and AUDIT (see below). Both CAGE and MAST are concerned with abnormal drinking behaviour such as drinking in the morning and alcohol-related problems rather than the level of consumption. The more recently developed AUDIT (Alcohol Use Disorders Identification Test) displays high sensitivity and has found increasing use in primary care; it is concerned with the level and frequency of consumption and adverse consequences.

CAGE asks four short questions.[20] CAGE is a mnemonic based on the key words in each question: Have you ever felt you should **C**ut down on your drinking? Have people **A**nnoyed you by criticizing your drinking? Have you ever felt bad or **G**uilty about your drinking? Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover ('**E**ye opener')?

Two or more positive answers are generally reliable in diagnosing alcohol dependence, and even one positive answer requires a more detailed clinical assessment. In clinical studies, sensitivities have been 60–95%,[20–23] specificities 40–95%.[24,25] A major criticism of CAGE is that a patient may score positive if he/she has religious concerns regarding alcohol, feels guilty even if he/she takes one drink, feels the need to cut down when drinking 'safe' amounts or is very health conscious.

A variant of the CAGE questionnaire is the T-ACE which has been shown to be particularly useful in the detection of heavy alcohol consumption in pregnant women.[26,27] In T-ACE, questions 2 and 4 are the same as in CAGE and score 1 point each. Questions 1 and 3 are as follows: (1) How many drinks does it take to make you feel high? (**T**olerance: the patient is considered tolerant if it takes more than two drinks to make her feel high, 2 points); (3) Have you ever felt you ought to **C**ut down your drinking? (1 point). A total score of $\geqslant 2$ points correctly identifies over 70% of heavy drinkers in pregnancy.

The Michigan Alcoholism Screening Test (MAST)[28] asks 25 questions which relate to

recognition of a drinking problem, help-seeking behaviour and alcohol-related disabilities.[29] Both sensitivity and specificity have been reported as 85%,[30] but other studies have yielded much lower figures than this.[31,32] There are several modifications of MAST. The Self-Administered Alcoholism Screening Test (SAAST),[33] an improved version of MAST, takes longer to administer and score (35 questions).

Developed by the WHO,[34] AUDIT's ten questions deal with quantity and frequency of alcohol consumption, symptoms of early and more established alcohol dependence, and the adverse consequences of drinking. Both sensitivity and specificity are 80–95%.[34,35]

Laboratory markers

Ideally, laboratory markers should reflect an individual's consumption of alcohol both chronically (screening marker) and acutely (relapse marker). A screening marker should display high sensitivity and specificity and discriminate between safe social drinking and heavy, hazardous drinking. The marker should not be elevated by non-alcohol-induced organ damage (particularly non-alcoholic liver disease) and should be non-invasive (e.g. urine, saliva, breath or blood test). A marker used to detect relapse should be sensitive to any consumption above safe levels. No such marker exists at present.

Laboratory tests are useful in helping to identify those drinking to excess, but they cannot diagnose alcoholism definitively. They can be used only to enhance suspicion and must be combined with a clinical history (including collaborative history from a relative if possible), physical examination, questionnaires and self-reporting. While some studies have shown laboratory markers to be less valuable than physical examination or questionnaires,[18,19] they do give objective information regarding alcohol consumption and changes in consumption over time, and they help the clinician decide on the possible role of alcohol in a clinical problem or disease process. They are also useful in following up an alcoholic patient and provide motivational input to the patient.

CONVENTIONAL LABORATORY MARKERS

Blood/urine/breath ethanol

Measurements of blood, urine and breath alcohol concentrations have a limited, but important, role. They provide no information regarding severity of alcohol drinking, but when positive do give objective evidence of recent drinking and can identify increased tolerance. Many heavy drinkers will abstain for 24 h before attending their physician, which results in a very low sensitivity to this test.

Serum γ-glutamyl transferase

Serum γ-glutamyl transferase (GGT) activity is increased in the serum in hepatobiliary disorders and with fairly heavy consumption of alcohol.[36] Serum levels of GGT have been found to be elevated in about 75% of individuals who are alcohol-dependent,[37–39] with a range in sensitivity of 60–90%.[40–42] The sensitivity is greatest when alcoholics and chronic heavy drinkers are compared to teetotallers and infrequent social drinkers.[43] In groups consuming hazardous amounts of alcohol but with no evidence of dependence, the sensitivities are much lower (20–50%), particularly in the primary care setting.[42,44–47] The increase in serum GGT in response to different amounts and duration of alcohol consumption varies considerably between individuals.[48] Consumption of > 40 g (> 5 units) of alcohol per day significantly elevates serum GGT in chronic alcoholics, whereas in previous non-drinkers at least 60 g/day for a minimum of 5 weeks is required before any increase occurs. GGT is rarely elevated in subjects under the age of 30 years and is less sensitive in women.[49]

In the general population, progressively higher serum GGT activities are associated with increasing levels of alcohol consumption. Elevated serum GGT is found in 20% of men and 15% of women who consume around 40 g alcohol per day and in 40–50% of men and 30% of women who drink more than 60 g/day. GGT is, then, primarily an indicator of chronic consumption of large amounts of alcohol and is not increased by binge drinking in non-alcohol abusers, unless there is concomitant liver disease. The half-life of GGT is between 14 and 26 days and its level usually returns to normal in 4–5 weeks after drinking ceases.[50]

As well as low sensitivity in some clinical situations, one of the major drawbacks to GGT as a marker of excessive alcohol consumption is its lack of specificity, which can vary from 55 to 100%. Numerous other disorders and drugs can elevate GGT and produce false positive results, including biliary tract disease, non-alcoholic liver disease, obesity, smoking, diabetes mellitus,

pancreatitis, hyperlipidaemia, hyperthyroidism, severe trauma, barbiturates, benzodiazepines, tricyclic antidepressants, anticonvulsants, anticoagulants, inflammation, clotting disorders, cardiac disease and renal disease.[51]

Despite its poor specificity, 50–72% of elevated GGT levels can be explained by excessive alcohol consumption.[40,52] A raised GGT in the absence of the obvious causes listed above should always raise the suspicion of excessive drinking, and a rapid fall in GGT with abstinence is highly suggestive that the initial suspicion was correct. Although GGT is not an ideal screening marker, it is useful in confirming a clinical suspicion of alcoholism and perhaps in monitoring abstinence in the recovering alcoholic.[53,54]

Serum transaminases

Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are often raised in patients who are alcoholics,[55,56] although generally not to more than 2–4 times upper normal limits; sensitivities are 25–60% for AST and 15–40% for ALT[42] (depending on whether the patients are known alcoholics or are being screened for high intake). Serum levels depend markedly on the degree of liver damage and how recently alcohol has been consumed. Acute alcohol intakes of 3–4 g/kg body weight can lead to moderate transient increases in AST in healthy subjects within 24–48 h. The AST:ALT ratio improves the test: a ratio > 1·5 strongly suggests, and a ratio > 2·0 is almost indicative of, alcohol-induced damage to the liver.[57] One study has shown the AST:ALT ratio to be the best of several markers at distinguishing between alcohol-induced and non-alcoholic liver disease.[58]

Mean corpuscular volume

An increased mean corpuscular volume (MCV) follows chronic heavy drinking and correlates with both the amount and frequency of alcohol ingestion,[53,59] but it can take at least a month of drinking more than 60 g alcohol daily to raise the MCV above the reference range.[59] It then takes several months of abstinence for MCV to return to normal,[60] so MCV has no role in monitoring abstinence or relapse. The actual mechanism by which alcohol causes an increase in MCV appears to include a direct toxic effect of alcohol on red blood cells, folic acid deficiency secondary to alcohol abuse and hepatic damage. Causes of a raised MCV other than excessive alcohol consumption include vitamin B_{12} deficiency, folic acid deficiency, hypothyroidism, haemolytic disease with associated reticulocytosis, non-alcoholic liver disease, anticonvulsants, azathioprine, zidovudine, age and smoking.

The main weakness of MCV is its low sensitivity both in hospital environments[42,61–66] and particularly in primary health care,[63,67–69] with an overall sensitivity of 40–50%, but its specificity is high (80–90%)[63,65,69,70] and very few tee-totallers and social drinkers will have elevated MCV values.

Lipids

Although increased high-density lipoprotein cholesterol or triglycerides can raise suspicion of excessive alcohol consumption, neither has sufficient sensitivity and specificity to be of use in diagnosis and monitoring.

Other markers

Serum IgA is classically raised in patients with alcohol-induced liver disease, as are urinary coproporphyrins. Serum urate is also raised in 20–40% of alcoholics. However, none of these markers is useful in screening for alcoholism or monitoring abstinence and all display inadequate sensitivity and specificity.

NEWER MARKERS

Serum mitochondrial AST

Serum AST consists of two isoenzymes: mitochondrial AST (mAST) and cytosolic AST (cAST).[71] In serum samples of normal healthy individuals cAST makes up > 90% of the total activity,[71] but when excessive alcohol consumption selectively injures mitochondria in the liver, mAST is preferentially released.[72] It is measured by an immunochemical technique in which specific antibodies precipitate cAST, leaving mAST to be measured using standard AST methods.[73] A sensitivity of approximately 90% in alcoholic patients has been reported,[74–76] although the specificity is low (in one study 79% of patients with non-alcoholic liver disease had elevated mAST).[75] The specificity was improved to 82% by using the mAST:total AST (mAST:tAST) ratio (cut-off 7%),[75] but with the consequence of lower sensitivity (range 52–100%).[74–76] The mAST:tAST ratio returns to normal levels within a few weeks of abstinence.

Like most other markers, both mAST and the mAST:tAST ratio have lower sensitivity (30–40%) in screening for hazardous drinking in the community and primary care.[77–79] The mAST:

tAST ratio can be particularly useful in a liver unit in helping to distinguish alcohol-induced from non-alcohol-related liver damage.

Serum carbohydrate-deficient transferrin

A component of serum transferrin that has an abnormally high isoelectric point – known as desialylated transferrin, later renamed carbohydrate-deficient transferrin (CDT) – was discovered in 1976 in the cerebrospinal fluid of alcoholic patients with cerebellar degeneration[80] and a few years later in the serum of alcoholic patients.[81–83] Transferrin exists in normal serum in various forms containing 0–9 sialic acid residues, predominantly tetrasialotransferrin (80%).[84–86] CDT consists of the asialo, monosialo and disialo isoforms, which are less negatively charged at pH 7·4. CDT was first proposed as a marker of excessive alcohol consumption in 1979.[87]

Alcoholic subjects consuming 50–80 g of alcohol per day for at least a week will show increased serum levels.[88] During abstinence CDT normalizes with a half-life of 15 days[88,89] and it thus remains elevated for several weeks. If drinking resumes, lower levels of alcohol intake can lead to a rapid re-elevation.[89] Initial studies assessing the alcohol-induced increase in CDT were conducted in alcoholics and chronic heavy drinkers in detoxification centres; in patients admitted to a general medical department, much more alcohol was required to increase CDT.[90] Furthermore, in healthy non-alcoholics, CDT failed to rise above the normal reference range after consumption of up to 80 g of alcohol per day for 3 weeks.[91,92]

CDT can be separated from transferrin by isoelectric focusing or chromatography.[88,89,93] A popular method of measuring CDT uses a competitive enzyme immunoassay kit (CDTect^{TM}) produced by Pharmacia Diagnostics (reference range up to 20 U/L in men, 26 U/L in women) or an Axis %CDT kit (turbidimetric immunoassay), when > 6% CDT:total transferrin is considered elevated.

Stibler's 1991 review[88] summarizing 20 studies involving 2500 established alcoholics calculated overall sensitivity as 82% and specificity as 97%. Subsequent studies showed that CDT was much better at detecting alcoholics than hazardous drinkers[63,89,94] and showed sensitivities in less extreme populations (e.g. women, general population, male university students, occasional heavy drinkers, college students, young male soldiers, healthy volunteers) of only 12–45%.[45,63,69,79,92,94–98] CDT is useless as a screening test for alcohol abuse; a recent meta-analysis of 110 clinical studies showed it to be no better than GGT in this respect.[99] In an attempt to compensate for the low sensitivity the CDT:total transferrin ratio has been proposed as a better marker.[100]

The main strength of CDT is its high specificity – 80–95% in the vast majority of studies[88,94–97] – but several conditions and diseases reduce this specificity. False positives can occur with: non-alcoholic liver disease (primary biliary cirrhosis,[101] chronic active hepatitis,[101] chronic hepatitis C[102] and hepatocellular carcinoma[103]); the genetic variant of transferrin known as D1 (found in 1% of the black population and < 1% in the white US population[104] and in up to 2% of Northern Europeans[105]); and the rare carbohydrate-deficient glycoprotein syndrome.[88,93]

One study has shown that patients who have undergone combined transplantation of the pancreas and kidneys had elevated CDT concentrations in the absence of alcohol consumption,[106] and increased CDT has also been seen in patients with cystic fibrosis due to defective sialylation.[107] Fagerberg *et al.* found that CDT levels may be altered by insulin-related metabolism (insulin sensitivity): male patients with hypertension who had elevated CDT concentrations had low blood glucose and serum triglyceride levels.[95,108] Other conditions associated with false positives are iron deficiency,[109] untreated galactosaemia,[110] rectal carcinoma, senile dementia, depression, pregnancy and solvent abuse.

In conclusion, CDT is of most use in monitoring patients for an increase in alcohol consumption or progressive abstinence.[111,112] A systematic review using the results of six prospective outcome studies with 239 male alcoholics found CDT to be significantly more sensitive than GGT in the detection of relapses.[113] It is of no use in screening for heavy alcohol consumption in the general population, particularly in women, and will not identify binge drinkers. However, a review of eight studies comprising 2214 patients found CDT to be better than GGT at distinguishing alcoholic from non-alcoholic liver disease.[113]

Serum/urine 5-hydroxytryptophd

Serotonin is normally metabolized to 5-hydroxytryptophol-3-acetic acid (5-HIAA) and 5-hydroxytryptophol (5-HTOL), with 5-HIAA being the major metabolite. Alcohol dose-dependently shifts serotonin metabolism towards 5-HTOL.[114]

The increase in 5-HTOL and decrease in 5-HIAA can be measured in both blood and urine using either gas chromatography or high-performance liquid chromatography (HPLC).[114,115] The 5-HTOL:5-HIAA ratio has been found to reflect alcohol intake in the past 24 h[115,116] and to remain elevated for 6–15 h after blood alcohol has returned to normal.[114] This potential marker has high sensitivity (as little as 20 g/day alcohol can be detected)[115] and specificity in detecting very recent alcohol consumption, and would be useful where frequent follow-up of patients is feasible and necessary. However, its method of measurement ensures that it will not be routinely used in the majority of laboratories.

Serum β-hexosaminidase

β-Hexosaminidase (β-HEX) is an acid lysosomal glycosidase. Increased serum and urine levels have been reported in alcoholic patients and in healthy volunteers after consumption of > 60 g of alcohol per day for at least 10 days, with sensitivities of 70–90%;[117–120] this is better than GGT and other established markers. However, like CDT, β-HEX appears not to be as effective in identifying less excessive but still harmful levels of drinking in unselected populations.[121] In alcoholics, β-HEX levels fall rapidly (7–10 days) to normal following abstinence. The β-HEX B isoform in particular is highly indicative of alcohol abuse.[122] Although high specificities (approximately 90%) have been reported for β-HEX,[44,120,122] serum levels of β-HEX have been noted to be increased in hypertension, diabetes mellitus, cirrhosis, pregnancy, in users of the oral contraceptive pill, cerebral infarction and myocardial infarction.[123–125] One of the major potential strengths of β-HEX is that it can be measured using standard and inexpensive laboratory techniques (spectrophotometry and fluorimetry). Its major isoenzymes can also be easily measured; isoform B is heat-stable whereas isoform A is heat-sensitive.[126]

Thus, serum β-HEX is a sensitive, easily measured, inexpensive test for excessive alcohol consumption, but like CDT it does not perform well in unselected populations; moreover, there are conditions other than alcohol intake that may cause it to be elevated.

Serum acetaldehyde and acetaldehyde adducts

Acetaldehyde, the first metabolite of ethanol, is not a good marker of alcohol consumption as it is metabolized to acetate within a few hours of consumption.[127] Acetaldehyde readily forms Schiff bases with amines and after irreversible rearrangement forms an acetaldehyde–protein adduct.[128]

Several proteins form adducts with acetaldehyde, including albumin and haemoglobin;[42,129,130] these can be measured either using HPLC techniques[131] or by detection of new epitopes created from the acetaldehyde–protein adduct using immunoassay.[132,133] Whole-blood-associated acetaldehyde (WBAA) includes both albumin and haemoglobin adducts, the concentration of the latter being 5–10 times higher than that of adducts with plasma proteins.[134,135] WBAA is affected by both acute and antecedent drinking behaviour; it returns to normal levels within 3 weeks of abstinence.[134,135] One drawback of this marker is that acetaldehyde can form in samples artefactually in the absence of alcohol intake.[136]

The haemoglobin–acetaldehyde adduct (HbA1-AcH) is detected in patients with excessive alcohol consumption with sensitivity 25–50%.[42,133,137,138] In patients admitted to a drug and alcohol rehabilitation unit, sensitivity was reported at 67% and specificity at 77%, better than GGT, AST or MCV; of these markers, HbA1-AcH was the only one significantly correlated with reported alcohol intake and with the theoretical ability to detect heavy hazardous drinking before the onset of liver damage.[139] Immunoglobulin A (IgA) reactivity with acetaldehyde-modified proteins has been shown to be elevated in both alcoholics and heavy drinkers, but not in social drinkers or patients with non-alcoholic liver disease.[140,141] However, in pregnant women who had abused alcohol, HbA1-AcH was inferior to both MCV and GGT in detecting excessive alcohol consumption or the adverse effects of alcohol on the fetus.[142]

Other markers

Other potential markers of excessive alcohol intake include fatty acid ethyl esters,[143] phosphatidylethanol,[144] sialic acid,[145] erythrocyte aldehyde dehydrogenase,[146] plasma α-aminobutyric acid: leucine ratio,[147] urinary salsolinol[148] and urinary dolichols.[149] Many of these require complex measurement techniques outside the capacity of the routine laboratory. All require further clinical evaluation, and none so far offers significant advantages over the existing established markers.

Combinations of markers

Attempts have been made to improve the sensitivity of single laboratory markers by

combining them, but although some of the combinations have shown enhanced sensitivity (e.g. CDT plus GGT, CDT plus MCV),[58,89,150–155] none has been widely accepted. Sophisticated mathematical treatment of results from multiple laboratory tests has also been proposed,[154,156,157] but the large number of test parameters required make the approach impractical, and in any case increased sensitivity invariably decreases specificity. Use of two or three different established markers appears to be optimal.

The Driver and Vehicle Licensing Agency (DVLA) has issued guidelines in connection with laboratory markers of excessive alcohol consumption (www.dvla.gov.uk/at_a_glance/ch5_drug_alcohol.htm, July 2001). Laboratory markers are primarily used here when a high-risk offender is being considered for the return of a suspended driving licence, to support a clinical history of either abstinence or controlled 'social' drinking. The Expert Medical Panel which advises the DVLA considers the most convenient markers to be the established ones of GGT, AST and MCV.

CONCLUSIONS

No laboratory test is reliable enough on its own to support a diagnosis of alcoholism; laboratory tests need to be part of a diagnostic process that includes a detailed clinical history and examination and the use of questionnaires. Laboratory markers are useful in both raising the suspicion and confirming the diagnosis of alcohol abuse; they are also helpful in the follow-up of patients undergoing treatment and in monitoring abstinence. However, sensitivities and specificities of the different laboratory markers vary considerably and depend on the population concerned. None has high accuracy in unselected populations in primary care settings and all are weak in screening for harmful heavy consumption of alcohol. The conventional marker GGT continues to remain the test combining greatest convenience and sensitivity. Its diagnostic accuracy can be enhanced by combination with other traditional markers such as AST, ALT and MCV. None of the newer markers offers significant advantage, although CDT seems to be better at monitoring patients for increased alcohol consumption or progress towards abstinence and possibly in distinguishing alcoholic liver disease from non-alcoholic liver disease.

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