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# Traditional markers of excessive alcohol use

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## ABSTRACT

**Aims** The blood tests used traditionally as markers of excessive drinking are the liver enzymes, gamma glutamyltransferase (GGT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and the red blood cell volume (mean corpuscular volume; MCV). Here we review the nature of these markers' association with alcohol use, their practical application in detecting, assessing or monitoring drinking and increases in understanding of these markers in the past 10 years.

**Design** Articles were identified via Medline search and perusal of bibliographies.

**Findings** The conventional markers have imperfect sensitivity and specificity, but have an added clinical role in the detection of complications of drinking, and of comorbid conditions that may increase risk of drinking. GGT may in part be a marker of the oxidative stress associated with ethanol metabolism. Markers are more likely to be elevated in those aged more than 30 years and in regular drinkers with a longer drinking history. The markers may be useful in opportunistic case finding, in motivating patients to change drinking and in monitoring treatment response. Increased prevalence of obesity and hepatitis C must be considered in interpretation of liver enzyme results. The liver enzymes are prognostic indicators for several medical conditions and for mortality.

**Conclusions** These conventional tests are widely available and relatively inexpensive. While having limited sensitivity and specificity in detection of excessive drinking, they also provide valuable data on complications of drinking, comorbid conditions that may be affected by drinking and, in some cases, prognosis.

**KEYWORDS** Alcohol drinking, biological markers/\*blood, erythrocyte indices, liver function tests.

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## INTRODUCTION

A wide variety of biochemical and haematological parameters are affected by regular excessive alcohol consumption. The blood tests traditionally used most commonly as markers of recent drinking are the liver enzymes, gamma glutamyltransferase (GGT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and the mean volume of the red blood cells (mean corpuscular volume; MCV). Other markers, including high-density lipoprotein cholesterol (HDL-C), triglycerides and uric acid may correlate with alcohol consumption, but are not sensitive or specific enough for use as single tests. Such markers may be useful, along with other clinical findings, in raising the

clinician's suspicion of excessive drinking, but are not the subject of this review.

In this report we review the published literature on the liver enzymes GGT, AST and ALT and on MCV as markers of alcohol use. Articles were identified via Medline search and perusal of bibliographies. It is not within the scope of this review to report on every one of the multitude of papers written on this topic: the focus is to review key findings, and in particular to review increases in understanding over the past 10 years. Testing for blood alcohol concentration is not addressed, as it is reviewed in a separate paper in this series. Except for the interpretation of different patterns of liver enzyme elevation, we will not address use of combinations of markers, as this will be

covered in a separate report. This review concludes with discussion of potential opportunities to gain additional value from these tests and need for further research.

There is considerable heterogeneity within the literature. The various markers have been studied in different populations and clinical settings and using different thresholds to define both abnormal tests and abnormal drinking. The purpose to which markers are applied is a factor in determining their usefulness. These may include detection of any alcohol consumption (for example in occupational testing of people on probation or before liver transplantation), binge drinking (which accounts for a significant proportion of the harms of alcohol abuse), hazardous or harmful alcohol consumption or alcohol dependence, detection of complications of drinking and also potentially identification of those most at risk from a set level of drinking.

Throughout this paper the term 'excessive drinking' is used to describe alcohol consumption that is above recommended limits. This could encompass hazardous, harmful or dependent drinking.

## THE LIVER ENZYMES: GGT, AST AND ALT

### GGT

#### *Brief description and history*

GGT is one of the longest established biochemical tests for excessive alcohol consumption [1]. GGT is a glycoprotein enzyme situated on the cell membrane in several tissues. It is possibly involved in reabsorption of glutathione from the glomerular filtrate and in protection against oxidative stress, via maintenance of intracellular glutathione levels [2]. Clinically, it has been used as a measure of liver function or damage, but it is also found in the kidney, brain, spleen, pancreas and heart [3]. This is one reason why increases in GGT are not specific for excessive alcohol consumption (see below). Hepatic GGT levels increase in response to exposure to a variety of drugs and to alcohol. This may be mediated via oxidative stress, with resultant reductions in glutathione levels. The metabolism of alcohol, for example, is known to result in free radical formation [4]. Normally, small amounts of GGT are released from the cell membrane into the circulation. In people with repeated excessive alcohol consumption, there may be increased release of GGT from the cell membrane. In cases with inflammation and liver cell damage, there may also be cell necrosis with release of the enzyme.

#### *Association with alcohol consumption*

Serum levels of GGT rise in response to alcohol consumption to a variable extent. The response varies between

individuals and within individuals according to the phase in their drinking history. GGT levels typically correlate only moderately with alcohol consumption ( $r = 0.30$ – $0.40$  in men,  $0.15$ – $0.30$  in women) [5], and there is some unpredictability about which drinkers will respond to excessive drinking with an elevation in GGT. GGT does not respond to a single dose of alcohol unless the person has previously been an excessive drinker [6–8]. GGT levels respond to even low levels of habitual drinking [5], but generally sustained excessive drinking is needed to rise a significant proportion of drinkers' levels above laboratory reference ranges. In experiments with volunteers, 60 g ethanol daily for 3 weeks produced no more than a 15% increase in enzyme levels [9] while 5 weeks produced almost a doubling of mean levels in young volunteers from 27 U/l to 52 U/l [10]. Regular drinking is more likely to increase levels than episodic drinking [11] and intensity of drinking (i.e. number of drinks per drinking day) appears to be important.

GGT increases more rapidly with resumption of alcohol consumption in those with a history of excessive drinking, and particularly if there has been a past raised GGT (see below) [12]. While GGT typically begins to fall within the first week of cessation of excessive drinking, the rate of decrease is variable, particularly in the presence of background hepatic impairment (see below).

#### *Applications*

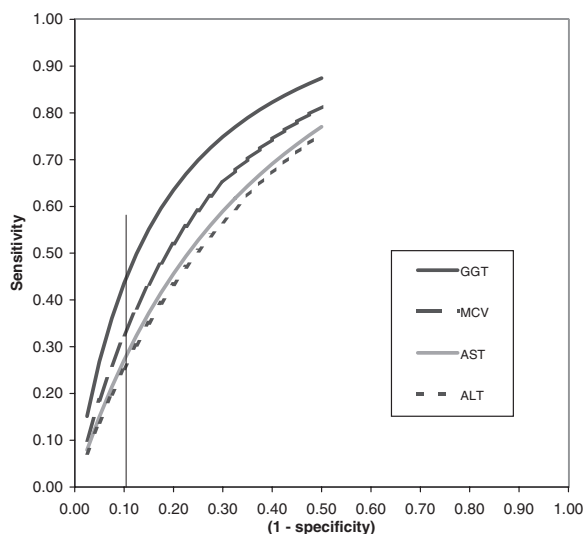
As with other markers, the clinical usefulness of GGT varies according to clinical context.

#### *Screening*

GGT is limited as a tool in screening by its relatively poor sensitivity. Only 30–50% [5,13,14] of excessive drinkers in the general community or family practice settings have elevated levels [11], although sometimes the proportion is less than 10% [15,16]. In these settings specificity varies from 40% up to nearly 90%. Sensitivity is similar in psychiatric in-patients (36%, specificity 87%) [17]. Sensitivity increases in medical in-patients (30–83%) [18–21] but non-alcohol-related illness and medication complicate interpretation of elevated test results, and accordingly specificities range from 75% down to 50% [18,19]. In residential alcoholism treatment units, sensitivity may be high (50–90%), with reasonable specificity (65–90%) [22–26] but in this setting a screening test is not needed. Because the sensitivity and specificity of GGT vary by setting, and performance may be enhanced when alcohol-dependent 'cases' are compared against light- or non-drinking controls, caution needs to be exercised so that results of comparisons between alcohol dependents

entering treatment and community controls are not used to assess GGT as a screening test.

A wide range of reference ranges for GGT have been used to define an abnormal test, ranging from 0 to 35 U/l to 0–80 U/l. Accordingly, it can be difficult to compare raw sensitivities and specificities from different studies. One technique which enables a comparison independently of threshold is to compare the Odds ratios of the test. The Odds ratio represents the product of true values of a test, divided by the product of false values of a test, i.e.  $(\text{true positive} \times \text{true negative}) / (\text{false positive} \times \text{false negative})$ . Across many studies the Odds ratios tend to be positively skewed, so to find a summary measure across studies we can first log-transform the Odds ratio from each study, then compute the mean of these values. The mean log Odds ratio from all relevant studies can be used to generate a summary receiver operator curve (ROC) [27]. Examples of this method are given in Scouller *et al.* 2000 [28]. Figure 1 shows the summary ROC values for GGT, MCV, AST and ALT in more than 50 studies conducted from 1993 onwards. Caution should be taken in interpretation as there was considerable heterogeneity in study characteristics, including factors such as age, recruitment site, severity of alcohol problems and gender. Furthermore, there were more studies that included GGT (>50) than other markers ( $n = 13$ ). It is provided here as a simple overview of the comparative performance of the markers across a range of studies. Further analysis would be required examining subsets of homogeneous studies, or just those studies that examined all four markers in the same subjects to provide more conclusive results.



**Figure 1** Comparative performance of GGT, MCV, AST and ALT across a range of studies conducted from 1993 onwards. Figure illustrates summary receiver operating characteristic curves. At 90% specificity, the sensitivities of the markers are: GGT 44%, MCV 33%, AST 27%, ALT 25%

### Opportunistic case finding

Because GGT is performed routinely as part of a biochemical test battery, there is considerable opportunity to use it for opportunistic case finding. Even though many factors can lead to an elevated GGT, alcohol is the most common cause. There are no data available on how efficiently abnormal GGT elevation is used in case finding, but research on other laboratory [29] and patient [30] clues to excessive alcohol use leads us to suspect it may be under-utilized [29].

### Assessment of physical complications of drinking and differential diagnosis

While GGT can be elevated in the absence of liver damage [31,32], it also tends to be the first test elevated in alcohol-induced liver damage [33]. GGT levels correlate with hepatic density on CT scan, which is a measure of liver fat content [34], and a trend for GGT levels to increase with increasing severity of damage on liver histology has been reported [31,35]. Together with the aminotransferases, albumin and bilirubin levels and clotting studies, the extent of test elevation can be used as a broad indicator of presence and severity of hepatic impairment. It should be noted that GGT levels can fall in more advanced cirrhosis. Between 5% and 20% of dependent drinkers with histologically normal liver show elevation of GGT, compared with more than 90% of dependent drinkers with cirrhosis [31,32,35,36]. However, as 40–100% of those with fatty liver and/or alcoholic hepatitis may also have GGT elevation [31,32,35,36] and tests may be affected by other causes of liver damage, only biopsy (where indicated) can determine the histology and extent of hepatic damage.

GGT elevation may also be a marker for other physical complications of alcohol use: excessive drinkers who have elevated GGT levels are more likely to also have hypertension than those drinking at the same level with normal GGT results [13]. GGT has been shown to be an independent predictor of future blood pressure and a rise in GGT is thought to be a marker of increased susceptibility to the pressor effects of alcohol [37,38]. Subjects with raised GGT are also more likely to have raised serum triglyceride [13] and to have neuropsychological impairment [39,40].

### Prognostic value

In addition to detecting current pathology, GGT levels have been reported to be predictive of future morbidity and mortality. GGT was shown to be predictive of all-cause mortality in three large cohorts of men [41–44]. In the Malmö study, Sweden, GGT results in the top decile for the community were also predictive of hospitalizations over the ensuing 4–7 years [45]. In male and female

trauma patients GGT levels predict increased complications of surgery [46]. GGT is a predictor of the subsequent development of hypertension [47–49], independent of baseline alcohol consumption, of diabetes [50] and of thrombotic stroke [51]. Pregnant women who have elevated GGT levels are more likely to deliver a baby with fetal alcohol syndrome [52], although sensitivity in predicting this condition is only 50% (for a specificity of 80%) in pregnant women drinking more than 100 g of alcohol per week [53].

It is not yet well understood why GGT acts as a marker and predictor of non-hepatic complications of alcohol use. It is possible that it is because it reflects a pattern of drinking that is more regular, higher quantity and/or intensity and of longer duration. This theory is supported by the fact that raised GGT levels also predict social consequence of drinking [48,54], including drink driving [54]. Alternatively, it has been proposed that a raised GGT may be a marker for susceptibility to the physical complications of drinking [2,13]. It may also act as a marker for oxidative stress, which may be one of the mechanisms by which complications occur [2]. In keeping with this last theory is the fact that GGT is also associated positively with cardiac ischaemia [55,56], a condition in which small amounts of alcohol have been shown to be protective.

#### *A tool in intervention*

GGT was used both as the prime method of screening and also as a tool in intervention in the Malmö study, Sweden [45,57]. Middle-aged men with GGT levels in the top decile were randomized to treatment or control groups. In the treatment group men were given counselling, and were informed of the link between their raised GGT levels and drinking. Every 3 months GGT results were fed back to the patient together with motivational counselling. The intervention group was found to have a significant reduction in sick leave, days of hospitalization and mortality compared to controls [45,57]. Similarly, GGT was used successfully as a component of screening and intervention in the Tromsø study in Norway [58]. Clinically, feedback of blood test results is useful both in motivating patients to change their drinking and in encouraging patients who have made progress, although no studies have established the extent of benefit over counselling alone.

*Monitoring treatment success.* GGT is used regularly both clinically and in research [59,60] to monitor response to treatment. Typically a reduction in GGT levels will be apparent from the first week of stopping drinking, and will be marked by the end of the first month [61]. The early reduction can help confirm a diagnosis of excessive

drinking. GGT levels typically fall halfway towards normal over 5–17 days of abstinence [62]. The fall towards normal takes longer in dependent drinkers, with a reported half-life of 26 days [63]. In those with hepatic damage (particularly cirrhosis) it may be still longer (range 11–54 days) [64] or may be incomplete.

Even when a drinker has a GGT within the reference range at baseline, following the individual's changes in levels may be useful [60,65] GGT levels are likely to increase 20–30% above the baseline in dependent drinkers who relapse (e.g. 50 g + ethanol on 2 + consecutive days) [60,66,67]. In one study, even a single dose of 1 g/kg ethanol after 4 weeks' abstinence was enough to result in a doubling of GGT levels (from 33 U/l to 69 U/l at 24 hours) in subjects who previously consumed 60–80 g of ethanol per day (baseline mean GGT of 86 U/l) [12]. Non-drinking controls had no significant increase in GGT. By comparison, in other studies patients who experience a slip, but not a full relapse (where a relapse is five or more standard drinks per day on 2 consecutive days), show a smaller (8%) and non-significant increase in GGT [66]. The rise in GGT with resumption of heavy drinking in dependent people is by no means universal. In a recent US study of 344 dependent drinkers in treatment, a rise in GGT of 30% above baseline occurred in only 29–32% of patients who relapsed (2 days or more of drinking five or more drinks per day), and rose by 30% without evidence of a relapse in 8–11% of patients [60].

#### *Strengths and weaknesses*

Because GGT is not only a marker of alcohol use, but also of hepatic damage, it has an important clinical role (see above). In addition to those listed above, a number of factors can influence test performance (Table 1).

#### *Factors that affect results*

GGT levels tend to increase with age, up to age 65 years, independent of alcohol consumption, and levels may then fall [5]. In parallel with this, GGT has been found to be of limited value in those aged less than 30 years [68–71], even when they have alcohol dependence [72]. GGT becomes a more sensitive marker of alcohol use with increasing age, but has been reported to perform less well in people aged over 60 in some [73,74] but not all [75] studies.

GGT levels may be raised above the reference range in persons with obesity, even in non-drinkers. Body mass index (BMI), or better the waist–hip ratio, has been reported to be a better predictor of GGT than alcohol [70]. With 20% of Americans being obese [76] and many other countries following suit, this is no longer a factor that can be ignored when interpreting liver enzyme levels, and in

**Table 1** Factors that influence marker levels.

GGT	AST	ALT	MCV
Less likely to be elevated in those aged less than 30, and possibly in the elderly	Less likely to be elevated in those aged less than 30, and possibly in the elderly	Less likely to be elevated in those aged less than 30, and possibly in the elderly	Less likely to be elevated in those aged less than 30, and possibly in the elderly
Men more likely to show test elevation			
May be more likely to be elevated in those of South Asian, African, Mexican or Brazilian descent	May be more likely to be elevated in those of South Asian, African, Mexican or Brazilian descent	May be more likely to be elevated in those of South Asian, African, Mexican or Brazilian descent	Some evidence that women may be more likely to show test elevation
Medical conditions			
Obesity	Obesity	Obesity	Folate or B <sub>12</sub> deficiency, including malabsorption
Liver and biliary conditions (including hepatic congestion)	Liver and biliary conditions	Liver and biliary conditions	Bleeding (leads to reticulocytosis)
hypertriglyceridaemia	Muscle diseases		Haematological conditions, including haemolysis, haemoglobinopathies,
diabetes pancreatitis	Extreme exertion		Marked increases in white cell count (15)
			Bone marrow disorders, liver disease
			Hypothyroidism
			Hyperglycaemia (115)
Medications			
Inducers of microsomal enzymes, e.g. anticonvulsants such as phenytoin, non-steroidal anti-inflammatories	A range of medications, drugs and herbal treatments can increase levels, including non-steroidal anti-inflammatory drugs, antibiotics, anti-epileptics	A range of medications, drugs and herbal treatments can increase levels including non-steroidal anti-inflammatory drugs, antibiotics, anti-epileptics	Medications that: produce marrow toxicity (e.g. chemotherapy, antivirals); alter folate metabolism, e.g. anticonvulsants, oral contraceptives, trimethoprim; impair cobalamin absorption (e.g. colchicine, neomycin) or utilization (e.g. nitrous oxide)
Other			
Smoking causes increased levels; inversely related to coffee (14, 94, 116), carbohydrate and fruit intake	Inversely associated with coffee (14, 94) intake	Inversely associated with coffee (94) intake	Smoking causes slight increase in level; inversely associated with coffee intake

particular GGT. GGT also responds more readily to alcohol consumption in obese people [77]: even 40 g ethanol per week can elevate GGT levels in the presence of obesity [14]. Obesity and alcohol have additive harmful effects on the liver so this is an important clinical finding, not just a false positive test result [78,79].

It is difficult to separate potential effects of race from influences of varying prevalence of viral illnesses, and environmental and cultural influences. Nonetheless, the prevalence of elevated GGT and aminotransferase levels has been found to be higher in South Asian excessive drinkers [80,81], in those of African [82,83] or Mexican [82] descent, and in Brazilian people [68].

A wide range of medications affect GGT, particularly those that induce the microsomal enzymes (Table 1). Any hepatic or biliary condition may affect GGT, including hepatic congestion in cardiac failure. Disorders of the other body sites where GGT is found can also affect levels (e.g. diabetes and pancreatitis).

### Availability

The GGT assay is cheap, widely available in automated form and routinely used for other purposes. If ordered as a stand-alone test it costs approximately US\$10–20, however if other biochemical measures are being ordered, the additional cost may be as little as \$1.

## THE AMINOTRANSFERASES

### AST and ALT

#### Brief description and history

AST (previously known as SGOT, serum glutamic-oxaloacetic transaminase) and ALT (also known as SGPT, serum glutamic pyruvic transaminase) are sensitive indicators of liver cell injury [84]. They are hepatocellular enzymes involved in amino acid metabolism. ALT is found

predominantly in the cytosol, whereas AST activity is highest in the mitochondria. The enzymes reach the circulation via the cell membrane, but there is poor correlation between degree of liver cell damage and aminotransferase level [85]. While present in the greatest concentration in the liver, AST is also present in heart, muscle, kidney, brain, pancreas, lung, leucocytes and erythrocytes [84]. Because of this, it has limited specificity for alcohol use. Because ALT is found predominantly in the liver it is affected less by non-hepatic insults [84].

#### *Association with alcohol consumption*

Like GGT, aminotransferases are not increased by a single episode of excessive drinking [8,12,86]. In eight young healthy male volunteers, consumption of 60 g ethanol per day for 5 weeks produced only slight rises in aminotransferases from the baseline and none were elevated above 30 U/l [10]. Probably a longer duration of drinking (and/or increased age of volunteers) would be more likely to result in increased levels. While AST values correlate highly with GGT values ( $r=0.61-0.68$ ), they do not correlate as highly with alcohol consumption ( $r=0.24-0.34$ ) [68].

#### *Applications*

*Screening.* The aminotransferases are less sensitive than GGT in detection of excessive alcohol consumption. Typically, less than half the subjects entering an alcoholism treatment unit have aminotransferases above the reference range, and in some samples the prevalence of positive results may be very low (e.g. 3/114) [26].

*Opportunistic case finding.* As with GGT, aminotransferases are often ordered as part of a battery of routine biochemical tests [84]. Alcohol is the most common cause of ALT elevation in otherwise healthy people. In a group of 100 blood donors with elevated ALT, alcohol was the most likely cause of elevation in half the cases, followed by obesity (22%), while 17–20% of donors were hepatitis C positive [87].

#### *Assessment of physical complications and differential diagnosis*

Like GGT, the aminotransferases act not only as markers of alcohol consumption but also as indicators of hepatic damage from alcohol. In one study 56% of subjects with ALT elevation had fatty liver on biopsy [88]. The aminotransferases may become elevated in the absence of cellular necrosis, and correlation between level of elevation and degree of cellular damage is poor [85].

The pattern and height of aminotransferase elevation assist in initial assessment of the nature of alcohol induced liver damage and in differential diagnosis. Typically, fatty liver is associated with minimally elevated aminotransferases, whereas these may rise to 500 U/l in alcoholic hepatitis. Higher aminotransferases suggest an additional or alternative liver injury such as drug or viral hepatitis. In viral hepatitis aminotransferases may reach considerable heights (>1000 U/l). GGT levels are typically higher than aminotransferase levels in alcohol-induced liver damage. When aminotransferases are elevated, if the AST : ALT ratio is greater than 2.0, 90% of cases are due to alcohol [89]. In contrast, in viral hepatitis the ALT is typically higher than the AST, and indeed there may be an isolated increase in ALT. While the pattern of results may assist in establishing which of two factors (alcohol or hepatitis C) is the predominant cause of hepatic impairment, whatever the cause, reduction in alcohol consumption or abstinence will be indicated.

Cirrhosis cannot be detected reliably by liver enzymes (see above). When advanced disease results in liver failure the GGT, AST and ALT are likely to fall, in the presence of reduced albumin and elevated bilirubin. The differentiation of these stages of alcoholic liver injury is difficult using non-invasive means, and liver biopsy remains the only accurate method.

#### *Prognostic value*

As with GGT elevation, AST levels have been found to be predictive of morbidity. In an Australian study, AST results above the 80th percentile (32 U/l) for an emergency department population were predictive of development of liver disease, gastrointestinal bleeding or trauma over the ensuing 3-year period [90]. This association was independent of alcohol intake, age and sex.

#### *Monitoring treatment progress*

An increase of 40% or more in AST level and 20% or more in ALT value has been reported to be suggestive of relapse to drinking in alcohol-dependent men (sensitivity and specificity >90% for AST ≥ 80% for ALT) [67]. This was true even if the marker remained within the reference range.

#### *Strengths and weaknesses*

*Factors which affect aminotransferase levels.* As with GGT, the aminotransferases are relatively insensitive to alcohol use in those aged less than 30 years [10,70,73,75]. They may also be insensitive in elderly drinkers (>70 years) [74].

Like GGT, the aminotransferases can increase with obesity or weight gain [70,91,92] and obesity may have a stronger correlation with ALT than alcohol [70]. As with GGT, aminotransferase levels have been reported to be higher in South Asian [80,81] and in Brazilian [68] excessive drinkers and in those of African [82,83] or Mexican [82] descent, but it is difficult to be sure if this is due to genetic or environmental influences.

Almost any medication can raise aminotransferase levels including antibiotics, antiepileptics, statins and non-steroidal anti-inflammatory agents [84,93]. Factors affecting muscle (e.g. strenuous exercise, muscle disorders) can also affect AST levels [84].

In a study of 2240 elderly subjects coffee consumption was inversely associated with ALT levels, and was a better predictor of ALT than was drinking of alcohol [94]. Coffee consumption is also inversely associated with AST [95].

#### *Availability*

As with GGT, assay of the aminotransferases is cheap and widely available.

## MCV

### *Brief description and history*

The mean volume of the red blood cell (mean corpuscular volume; MCV) has been recognized for many years as increasing with excessive alcohol consumption [96]. In alcohol excess, the majority of cases of macrocytosis occur in the presence of normal folate levels [96,97] and without anaemia, and do not respond to folate treatment [96]. The cause of macrocytosis is complex. Ethanol appears to have a direct marrow toxic effect, causing reduced marrow cellularity and vacuolization of red cell precursors, similar to that seen in chloramphenicol toxicity [98]. In 30% of dependent drinkers with increased MCV there will be some reduction in folate levels [96]. This may be due to dietary deficiency, impaired absorption or increased excretion, [98,99] but in only 17% of cases of alcoholic cirrhosis will there be actual folate deficiency (serum folate < 2.5 ng/ml) [97]. Ethanol also appears to have a specific antifolate action [98]. A variety of other red cell changes may occur in association with alcohol dependence, such as sideroblastic anaemia [96,98,100] and, particularly in alcoholic cirrhosis, occurrence of spur cells and stomatocytes [96,98,100–104]. MCV levels may also become elevated with liver disease of any cause, due to altered synthesis or increased destruction (haemolysis) of red cells in the congested spleen [97]. Furthermore, occult bleeding is common in alcohol dependence. Either haemolysis or bleeding

results in increased numbers of young red cells (reticulocytes) with larger cell volume.

### *Association with alcohol consumption*

As the life-span of a red blood cell is 120 days, it may take several months for changes in drinking to be reflected in MCV levels [105]. Sustained and regular excessive drinking appears to be needed to result in elevated MCV levels in the absence of folate deficiency, liver disease or bleeding. There are no experimental studies demonstrating an increase in MCV with administration of alcohol in healthy volunteers. Regularity of drinking is important. Meerkerk demonstrated that no irregular excessive drinkers (60 g + per occasion) in a family practice setting had increased MCV, while 33% of those drinking 20 times or more per month did [11]. In alcohol dependence, MCV levels may continue to rise upon cessation of drinking [61]. This may be due in part to increased numbers of reticulocytes, as the marrow begins to recover [98].

### *Applications*

*Screening.* MCV has limited value as a single marker in screening because of its poor sensitivity, typically below 50%. In one general practice setting MCV detected less than 20% of excessive drinkers [11]. On the other hand, MCV is more specific than GGT in most populations. In Meerkerk's general practice study MCV had specificities of more than 90% [11]. In medical in-patients sensitivity tends to be higher, but specificity lower (sensitivities of 52–75% for specificities of 85–74%) [19,20]. Despite these limitations, MCV may be the best of the traditional markers in screening for excessive drinking in women.

*Opportunistic case finding.* MCV is a test that is performed so commonly that there is opportunity to use it in opportunistic case finding. Approximately 3–5% of out-patients will have elevated MCVs and alcohol is the most common cause for this [29]. However, currently 50% of elevated MCV levels are not followed-up by the treating doctor [29].

### *Assessment of complications and differential diagnosis*

While in most cases of excessive drinking macrocytosis occurs without folate deficiency or other medical disorders, a raised MCV may sometimes reflect complications of drinking including folate deficiency [96–98]. In this case, the MCV may not return to normal even in the face of prolonged abstinence. In liver disease the presence of haemolysis and anaemia may reflect liver cell dysfunction [97]. Macrocytosis may also reflect new red cell formation after occult gastrointestinal bleeding.

Macrocytosis can occur in liver disease of other causes, in bleeding, vitamin (B<sub>12</sub> or folate) deficiencies and in a variety of haematological conditions, and in association with several common medications that alter folate metabolism (Table 1). Macrocytosis or macrocytic anaemia is more than twice as common in alcoholic cirrhosis than in other forms of cirrhosis (76% versus 30% for macrocytosis and 50% versus 17% for macrocytic anaemia, respectively) [97].

#### *Prognostic value*

MCV has been found to be significantly higher in women who have miscarriages than matched controls [106] and is highly specific but poorly sensitive in predicting occurrence of foetal alcohol syndrome [52,53](see below). It is hard to ascertain whether these effects are independent of the effects explained by alcohol consumption.

#### *Monitoring treatment progress*

Because of its slow response to changes in drinking, MCV is generally unsuitable as a marker of short-term progress [61,107]. It has been proposed that if bloods cannot be taken for liver enzymes at the time drinking first stops, MCV can be useful in reflecting earlier drinking [108]. However, in the first week of treatment there can be alterations to MCV. Interestingly, in some cases of cirrhosis, MCV may begin to fall even after 1 week's abstinence, [97] perhaps pointing to improvement in more rapidly reversible factors such as red cell destruction. In other cases MCV may rise in the first week, as erythropoiesis increases [98].

#### *Strengths and weaknesses*

*Factors which affect performance.* As with the liver enzymes, MCV may have a poor sensitivity in those aged less than 30 [69]. It becomes more sensitive with increasing age throughout most of adulthood [70,75] although may be of limited value in detecting excessive drinking in the elderly. In one study of 162 medical in-patients aged 65–99 years, MCV detected less than 20% of excessive drinkers [109]. In contrast, in another study of medical in-patients and elderly people living in the community, sensitivity and specificity in elderly patients were both in the 60s [74]. The reason for these differences is not clear.

Several authors have reported MCV to be more sensitive in women than in men [70,110].

#### *Availability*

MCV measurement is widely available, and MCV is generally measured routinely wherever a full blood count is

requested. Automated cell counts are more accurate than manual methods [111].

#### **Need for further research**

It is still poorly understood why one drinker will respond readily to drinking with GGT or other marker elevation and others will have no elevation despite excessive drinking. The evidence of the markers' prognostic significance raises the question of whether the marker elevation is an indicator of increased susceptibility to the physical complications of alcohol, or just an indicator of the pattern of drinking more likely to result in harm. Genetic and other determinants of responsiveness of markers to alcohol use will be of interest and may have longer-term applications in tailoring intervention intensity or type to those most at risk of harm.

We are only just beginning to understand the mechanisms by which GGT levels rise in response to excessive alcohol consumption in some people. Given the associations between GGT and morbidity and mortality, understanding these mechanisms further may lead to better understanding of the pathophysiology of alcohol-related harm. Similarly, the precise mechanism by which alcohol interferes with red cell formation in the bone marrow is still poorly understood.

There have been a large number of recent studies pointing to independent associations between GGT levels and indicators of cardiovascular risk, including insulin resistance. In order to understand better the complex interactions between alcohol, liver enzymes and health there is a need for large, well-constructed prospective studies to elucidate better the associations between liver enzymes and future health. Such studies require detailed information on factors which may influence both the enzymes and health, including body mass index (or waist–hip ratio), smoking, viral hepatitis markers and age. Given the evidence of the importance of pattern of drinking both on marker levels and on the risk of harms or benefits of drinking, future research should consider the impact of pattern and duration of drinking on markers and other health risk factors.

Reference ranges vary widely around the world; for example, the upper limits for GGT vary from 25 U/l to 80 U/l. There is need to research the optimal reference range taking into consideration not just level of alcohol consumption, but association with and risk of physical complications (see discussion in [112]). It may be that different reference ranges may be indicated for different purposes. Whether there should be also a mechanism for adapting automatically the reference range for the age and gender of the subject is another issue which has not yet been explored. Further research is needed to establish if the markers are useful in those aged over 65 years. This



is particularly relevant in view of the recognition of the ageing of the population in developed countries, and the fact that that alcohol abuse is becoming increasingly common in this age group.

Research into the practicality of routine application by laboratories of computer algorithms to enhance reporting and interpretation of laboratory results by combining markers and by considering the age and sex of the subject needs consideration. Alternatively, electronic desktop algorithms could be used to allow clinicians to factor in influences such as obesity and smoking in determining the appropriate reference range for their subject.

The rising prevalence of hepatitis C linked to increases in intravenous drug use has created new challenges in interpreting liver enzyme results. Currently 2.7 million Americans have chronic hepatitis C infection and 1.8% of the US population have been infected at some time [113]. It is particularly important to be able to detect hazardous drinking in those with active hepatitis C, fatty liver or other liver disease in order to warn the drinker of the danger of compounding harm to the liver. Few alcohol marker studies have been able to assess prevalence of viral hepatitis in their samples, even though there is recognized comorbidity between alcohol dependence and other substance abuse or dependence. Recent studies have investigated the ratio of GGT to ALT as a method for predicting response to antiviral treatment [114]. We were unable to locate any data on GGT:ALT ratio as a method of assessing contribution of alcohol versus virus to liver impairment. As interferon treatment is associated currently with unpleasant side effects, it would be useful to be able to identify better those cases where, despite the presence of hepatitis C virus, the damage to the liver will be minimal if drinking is stopped. We need to determine more effectively what are safe levels of drinking in those with coincident liver disorders, and how the markers might be best used in this context to assess prognosis and monitor progress.

## CONCLUSIONS

While the traditional markers of alcohol use, GGT, AST, ALT and MCV, have limited sensitivity and specificity, they remain useful adjuncts in the assessment and management of excessive drinkers. Their levels may indicate complications of drinking, or concurrent conditions that may be affected by drinking. Monitoring changes to an individual's levels of GGT can assist in both in assessing treatment outcome and in providing feedback to the patient, which may help maintain enthusiasm for change. GGT in particular has a complex association with health and raised levels are predictive of a broad range of adverse health outcomes. There is still a need for

ongoing high quality research to maximize the value that can be obtained from the traditional markers and to deal with the changing demographics and background comorbidity of our population.

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