Prediction of Alcohol-Related Harm by Laboratory Test Results

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We examined the value of laboratory markers of excessive alcohol (ethanol) intake as predictors of mortality, morbidity, and health-care utilization in a cohort of 330 patients attending an acute ambulatory care service. Among men, all four markers examined—γ-glutamyltransferase (GGT) and aspartate aminotransferase (AST) activities, high-density lipoprotein cholesterol (HDL-C), and mean corpuscular volume (MCV)—were predictive of medical sequelae and health-care utilization over a 3-year period. In contrast, social problems were more closely related to the amount of alcohol consumption at initial assessment than to any biological marker. Serum GGT and AST activities and MCV were predictive of medical sequelae in women. The predictive value of GGT was an independent risk factor and did not merely reflect recent alcohol intake or the presence of chronic liver disease. We conclude that these readily available laboratory tests provide important prognostic information and should be an integral part of the assessment of persons with hazardous alcohol consumption.

Indexing Terms: alcoholism · γ-glutamyltransferase · aspartate aminotransferase · lipoproteins · cholesterol · erythrocyte

Excessive consumption of alcohol (ethanol) may lead to a variety of gastrointestinal neurologic, cardiovascular, and malignant diseases. It is associated with a three- to sevenfold increase in premature mortality (1–3), and imposes a heavy economic burden (4–6). However, alcohol-related diseases are not observed in everyone who drinks hazardous amounts of alcohol, and it would be useful to have tests by which one could predict their occurrence. Relying on an individual's history of alcohol consumption is inadequate. Although epidemiological studies have shown that alcohol intake correlates with risk of cirrhosis (7) and is a predictor of other physical harm (3), there are difficulties in determining the amount consumed. Such data are critically dependent on the accuracy of self-reporting. There is also a wide variation in the amount of alcohol consumed before adverse consequences occur.

Several biochemical and hematological tests, such as γ-glutamyltransferase (GGT; EC 2.3.2.2), aspartate aminotransferase (AST; EC 2.6.11), high-density lipoprotein cholesterol (HDL-C), and erythrocyte mean corpuscular volume (MCV) are established markers of alcohol intake (6). Their validity as markers is based largely on correlations with recent intake at a single time point and on decreases in elevated values when heavy drinkers abstain from alcohol. In two prospective studies, increased AST activities were predictive of cirrhosis (8), and abnormal GGT results were associated with increased mortality and hospitalization (2). However, the broader prognostic significance of these tests has not been evaluated, nor has their usefulness as predictors been compared with that of self-reported intake.

In this study we examined the value of laboratory tests as predictors of three end points—illness, social problems, and health-care utilization—in patients attending an acute ambulatory care service. We addressed the following issues: Are GGT, AST, HDL-C, and MCV useful predictors of these end points? Are they valid predictors across a range of age groups and in both men and women? Do they function merely as proxies for excessive alcohol consumption in predicting harm or do they have intrinsic prognostic significance?

Materials and Methods

Recruitment and Initial Interview

In 1984–85 we interviewed 350 patients who were attending the ambulatory care section of the Emergency Department of Royal Prince Alfred Hospital, Sydney. Subjects not currently being attended by a medical officer were approached in sequence. There was an 11% refusal rate. Informed consent was obtained, and all procedures were in keeping with the ethical standards laid down by the Royal Prince Alfred Hospital Ethics Review Committee. Each individual underwent a comprehensive assessment of medical history, alcohol consumption, and related problems with use of the questionnaire devised for a recent World Health Organization study (9–11). Clinical examination was performed, and blood was taken for measurements of GGT, AST, HDL-C, and MCV. The prevalence of hazardous alcohol consumption and related problems in this sample was reported previously (11). At the end of the interview, subjects were asked permission to be contacted after 2–3 years; 12 subjects refused. Eight further subjects were excluded from the longitudinal study because of malignant disease present at the initial inter-

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6 Nonstandard abbreviations: GGT, γ-glutamyltransferase activity; AST, aspartate aminotransferase activity; HDL-C, high-density lipoprotein cholesterol concentration; MCV, erythrocyte mean corpuscular volume; RR, relative risk, and CI, 95% confidence interval.
view. This left a cohort of 330 subjects, comprising 212 men and 118 women.

Laboratory Methods

GGT and AST were measured by standard methods on a Technicon SMAC (Tarrytown, NY), HDL-C was measured by an enzymatic assay on an IL Multistat (Instrumentation Laboratory, Lexington, MA) after precipitation of other lipoproteins by dextran sulfate/magnesium chloride, and MCV was measured with a Coulter S+ (Coulter, Hialeah, FL).

Follow-up Assessment

Two years after the initial assessment, the subjects were invited to a follow-up interview. Of the cohort of 330 subjects, 250 (76%) were either reinterviewed (72%) or found to be deceased with cause of death known (4%). Of those interviewed, 81% had a personal interview, 18% were interviewed by telephone, and 1% by mail. Interviewers were blind to the results of the initial assessment. For each subject the interviewer recorded experience of alcohol-related physical and social problems, number of hospitalizations, and attendances for medical consultations in the period between interviews [mean (±SD) period, 32.2 ± 5.8 months]. Alcohol intake was reassessed. The final part of the assessment involved inspection of subjects' medical records at Royal Prince Alfred Hospital and neighboring hospitals. Records were found for all except three subjects. Each hospital attendance was coded according to whether it was definitely or possibly related to alcohol. Coding was done by a registered nurse who was blind to the initial interview results and used a list of diagnoses and situations we compiled (criteria available on request).

Definitions

A score for medical illnesses was computed by adding one point for each of the following conditions experienced since the time of initial interview: liver disease, gastrointestinal hemorrhage, head injury, road accident injury or fractures, hypertensive medication in the past week, and elevated blood pressure (≥140/90 mm Hg) (12) at follow-up interview. These conditions were considered to be those most likely to be related to alcohol use in this population. Experience of trauma was assessed by asking if the subject had broken any bones, had a head injury, or been hurt in a road accident. A social problem scale was compiled from the following: friends or family concerned about drinking, employer or workmate concerned about drinking, work problems related to drinking, and legal problems due to drinking. Each item contributed one point to the score. A health-care utilization score was computed by adding coded values for the number of hospital admissions and the frequency of general practitioner attendances and of specialist consultations, all as reported in the interview.

Analysis

Of the 330 subjects, liver enzyme results were unavailable for 9, HDL-C results were unavailable for 12, and MCV results were unavailable for 6. These subjects were excluded from analyses relating to those tests. Results for GGT and AST were excluded in individuals with biliary disease or liver disease with known cause other than alcohol; MCV results were excluded in subjects with anemia or hemoglobinopathy.

For each biological marker, the decile values were established for both sexes. Subjects in the top two deciles (i.e., above the 80th percentile) and the top decile were then compared with those below the median. Linear multiple regression was performed to examine the interrelations among blood test results, alcohol intake, and health-care utilization in the entire sample. Because scores for alcohol-related illnesses and social problems were too highly skewed to be satisfactorily transformed, they were dichotomized according to the presence or absence of harm and analyzed by logistic regression. Liver enzyme results and alcohol intake were log10-transformed for all regression analyses. All values for relative risk (RR) quoted are statistically significant (the 95% confidence interval (CI) excludes 1.0) unless otherwise stated.

Most of the analyses were performed on the Statistical Package for the Social Sciences SPSS® Version 2.2 (13). Logistic regression was performed on BMDP, Version PC90 (14), and RRs for 2 × 2 tables were calculated by using EPI 5 (15).

Characteristics of Subjects Lost to Follow-Up

Those who, at the time of the initial interview, refused participation in the follow-up study were not among the heaviest drinkers. Indeed, they had lower GGT concentrations (P < 0.05) and a tendency toward a lower alcohol intake than those who remained in the study. In contrast, those who were later lost to follow-up were more likely to have consumed hazardous amounts of alcohol (>40 g/day for a man and >20 g/day for a woman) compared with those who were reinterviewed (40.0% vs 17.2%, P < 0.001).

Results

Experience of Mortality, Alcohol-Related Illnesses, and Social Problems

Over the follow-up period, 12 subjects (11 men, 1 woman) died. A total of 120 subjects (84 men, 36 women) reported having an illness that could be related to alcohol over the follow-up period, of whom 24 (21 men, 3 women) had liver disease or gastrointestinal hemorrhage, 56 (41 men, 15 women) had experienced an episode of trauma, and 77 (56 men, 21 women) had elevated blood pressure at the follow-up interview. Social problems related to drinking were reported by 59 subjects (51 men, 8 women).

Laboratory Results as Predictors of Mortality, Alcohol-Related Illness, and Social Problems

Table 1 presents the RR values for mortality, alcohol-related illnesses, and social problems among men, comparing those who had GGT, AST, HDL-C, and MCV results and alcohol intakes above the 80th percentile

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Table 1. Relative Risk of Death, Medical and Social Consequences, and Hospitalization among Men, in Relation to Laboratory Test Results and Alcohol Intake at Recruitment

<table>
<thead>
<tr>
<th>Medical disorders</th>
<th>GGT, U/L</th>
<th>AST, U/L</th>
<th>HDL-C, mmol/L</th>
<th>MCV, fl</th>
<th>Alcohol intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver disease or gastrointestinal bleeding</td>
<td>4.9*</td>
<td>4.1*</td>
<td>2.2</td>
<td>9.3*</td>
<td>4.3*</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>1.5</td>
<td>1.0</td>
<td>0.8</td>
<td>1.1</td>
<td>1.8*</td>
</tr>
<tr>
<td>Trauma</td>
<td>1.8*</td>
<td>2.5*</td>
<td>1.6</td>
<td>2.4*</td>
<td>1.5</td>
</tr>
<tr>
<td>Social problems related to alcohol</td>
<td>1.2</td>
<td>1.4</td>
<td>1.7</td>
<td>2.0*</td>
<td>4.7*</td>
</tr>
</tbody>
</table>

* Significant increase in risk (95% CI excludes 1.0).

Relative risk was calculated by comparing experiences over the 3-year follow-up period of men who initially had a test result or intake in the top two deciles with those whose values were below the median.

Table 2. Absolute Values Corresponding to 50th, 80th, and 90th Percentiles in Distribution of Laboratory Tests and Alcohol Intake in Men

<table>
<thead>
<tr>
<th>GGT, U/L</th>
<th>AST, U/L</th>
<th>HDL-C, mmol/L</th>
<th>MCV, fl</th>
<th>Alcohol intake, g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>40</td>
<td>0.96</td>
<td>90</td>
<td>13</td>
</tr>
<tr>
<td>80</td>
<td>48</td>
<td>1.30</td>
<td>93</td>
<td>51</td>
</tr>
<tr>
<td>92</td>
<td>84</td>
<td>1.57</td>
<td>95</td>
<td>115</td>
</tr>
</tbody>
</table>

Table 3. Absolute Values Corresponding to 50th, 80th, and 90th Percentiles in Distribution of Laboratory Tests and Alcohol Intake in Women

<table>
<thead>
<tr>
<th>GGT, U/L</th>
<th>AST, U/L</th>
<th>HDL-C, mmol/L</th>
<th>MCV, fl</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>25</td>
<td>1.17</td>
<td>89</td>
</tr>
<tr>
<td>37</td>
<td>32</td>
<td>1.50</td>
<td>93</td>
</tr>
<tr>
<td>47</td>
<td>42</td>
<td>1.75</td>
<td>95</td>
</tr>
</tbody>
</table>

with those who had values below the median. The percentile values for each marker are shown in Table 2. Among men, GGT, AST, and MCV results above the 80th percentile were good predictors of liver disease, gastrointestinal bleeding, and trauma. GGT was a significant predictor of mortality and MCV predicted alcohol-related social problems. These findings were magnified when we compared only subjects whose results were above the 90th percentile with those whose results fell below the median. On the basis of the GGT results, the RRs of death, liver disease, and gastrointestinal bleeding and trauma were 12.1, 8.1, and 2.4, respectively. The results for MCV indicated RRs of liver disease and gastrointestinal bleeding and trauma of 14.6 and 3.7, respectively; and with the AST results, the RR for liver disease and gastrointestinal bleeding was 8.7. In addition, serum AST above the 90th percentile was predictive of death (RR = 3.6). An HDL-C result above the 90th percentile was predictive of liver disease and gastrointestinal bleeding (RR = 3.5). The best predictor of social problems in men was self-reported alcohol intake at initial assessment.

Among women, a GGT or AST result above the 80th percentile was associated with an increased risk of high blood pressure (RR 2.5 and 2.3), and MCV was associated with increased risk of trauma (RR 3.1). The percentile values for each marker are shown in Table 3. HDL-C and alcohol intake in the top two deciles were not significant predictors of any of these end points in women. No additional associations with medical sequelae were found in women with results above the 90th percentile.

The overall association between laboratory test results and experience of alcohol-related illnesses is illustrated in Figure 1, which depicts illness scores for quintile groups for each test for men and for women across the entire sample.

Regression analyses were used to determine the extent to which the predictive value of laboratory tests was independent of alcohol intake in the whole sample. Using logistic regression, we found that each unit increase in log10GTT (e.g., an increase in GGT from 10 to 100 U/L) was associated with a 13.4 times increased risk of experiencing an alcohol-related illness. The risk remained high after controlling for age, sex, the number of cigarettes smoked per day, body mass index, and mean daily alcohol intake. When all these confounding variables were entered, the RR was still 9.3 (95% CI 2.4–35.1). Controlling for frequency as well as quantity of alcohol intake at recruitment did not reduce the predictive effect, nor did excluding all known alcoholics (19 alcoholics excluded, 219 subjects remaining in analysis). Each unit increase in log10AST was associated with an 11.9 times increased risk of experiencing medical disorders. When alcohol intake was controlled for, the RR remained significant at 7.0. Using the logistic regression model, we found that MCV and HDL-C were not significant predictors of morbidity once age, sex, and alcohol intake were controlled for.

Laboratory Results as Predictors of Health-Care Utilization

Over the follow-up period, 216 subjects (128 men and 88 women) had seen a physician, and 115 (70 men, 45 women) had been admitted to a hospital. Thirty-two subjects (29 men, 3 women) had attended the emergency or outpatient departments of the Royal Prince Alfred Hospital with an alcohol-related disorder.

Among men, those with GGT and HDL-C results above the 80th percentile had an increased likelihood of admission to hospital (RR = 1.7 and 1.6, respectively) and of outpatient attendance at Royal Prince Alfred Hospital with an alcohol-related disorder (RR = 3.2 and 1.9). Those with an MCV above the 80th percentile had an increased risk of an alcohol-related attendance (RR = 6.0). If only the top decile was examined, MCV as well as GGT and HDL-C were predictors of admission to
hospital (RR = 1.7, 2.2, and 1.9). GGT and MCV results above the 80th percentile were predictors of overall health-care utilization on the basis of the composite score (RR = 2.4 and 1.7, respectively). Those with HDL-C results in the top decile also had increased health-care utilization (RR = 2.4).

Applying multiple regression analysis to the data from all subjects, we found that GGT was a significant predictor of health-care utilization in both sexes and remained so after controlling for alcohol intake, age, sex, cigarettes smoked, and body mass index. GGT remained a predictor when subjects with known chronic liver disease (n = 2) were excluded from analysis and also when all known alcoholic patients (n = 19) were excluded.

Discussion

We have demonstrated that several laboratory markers of alcohol intake are of value in predicting adverse health outcomes. Among men, all four markers (GGT, AST, HDL-C, and MCV) were predictive of increased risk of death or the medical sequelae of alcohol consumption. In addition, all markers except AST were predictive of the number of hospitalizations and outpatient attendances for alcohol-related conditions and of overall health-care utilization. Social problems were more closely associated with the level of alcohol intake than with a particular biological marker. Among women, GGT and AST were predictive of hypertension, and MCV was predictive of trauma. However, these findings must be interpreted with caution, because the total number of women experiencing medical disorders was comparatively small.

Despite the fact that the laboratory tests examined in this study have been recognized as markers of alcohol intake for up to 20 years, there have been surprisingly few studies of their prognostic significance. Kristenson (2) and Peterson et al. (16) demonstrated that a GGT result in the top decile was predictive of mortality and increased hospitalization in Swedish middle-aged men. A high GGT concentration was also found to predict increased fractures in a sample of adult men (17). The predictive effect of GGT was assumed to reflect these subjects' heavy drinking (2). However, this was not examined empirically and, indeed, only 54% of the Swedish subjects with GGT results in the top decile admitted to drinking >40 g of alcohol per day (2). AST has been identified as a predictor of cirrhosis in alcoholics (3), but we found no reports on its broader prognostic value. Likewise, while the association between high HDL-C values and reduced incidence of ischemic heart disease (18) has been a subject of great interest, the general prognostic significance of HDL-C has had little study. Similarly, there is no information on the predictive value of MCV for overall morbidity and mortality.

Our results raise several questions. Do these markers merely reflect actual alcohol intake better than the subjects' own report? Our findings do not support this contention: the markers were better predictors of alcohol-related medical disorders than reported intake, whereas reported intake was a better predictor of social problems. Do the markers reflect a particular pattern of drinking that is more likely to lead to physical harm? At least for GGT, this does not explain the findings adequately, because the relation between the GGT score and alcohol-related illnesses remained significant after both mean daily intake and frequency of drinking were controlled for. Those drinkers who have marker abnormalities may well have incipient tissue damage, but it is also possible that this group has an inherent biological susceptibility to the tissue-damaging effects of alcohol. Some of the findings may reflect increases in subjects' alcohol intake between recruitment and follow-up interviews. This was not assessed directly, but it does not detract from our findings that these markers are useful predictors of alcohol-related mortality, morbidity, and health-care utilization.

Alcohol-related problems place a major burden on the health-care system and on the national economies of many countries, and are responsible for much suffering at an individual level (4–6, 19). However, effective interventions for hazardous and harmful alcohol consumption are now available, and there is evidence that treatment is cost-effective (2, 20). The results presented
here indicate that abnormal GGT results in men and women, and abnormal AST, HDL-C, and MCV results in men, are valuable predictors of alcohol-related medical disorders and of health-care utilization. For example, a man with a GGT result of >80 U/L has a sevenfold increased risk of death over the next 3 years, a fivefold increased risk of liver disease, and a twofold increased risk of trauma compared with a man with a GGT result <30 U/L. A man with an MCV of >93 fl has a ninefold increased risk of liver disease or gastrointestinal bleeding over the next 3 years compared with a man with an MCV result <90 fl. Among women, the predictive values appear to be somewhat less; nonetheless, GGT, AST, and MCV were more strongly associated with medical sequelae than was the level of alcohol intake. These markers therefore have considerable potential in screening for those at greatest risk of medical complications of drinking. In two early intervention programs, feedback of abnormal laboratory results to patients was used to help motivate subjects to change their drinking patterns (2, 21). The results of the present study provide important information that strengthens the rationale for doing so.

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