Relationship Between Alcohol Drinking and Aspartate Aminotransferase:Alanine Aminotransferase (AST:ALT) Ratio, Mean Corpuscular Volume (MCV), Gamma-Glutamyl Transpeptidase (GGT), and Apolipoprotein A1 and B in the U.S. Population*

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ABSTRACT. Objective: The misuse of alcohol, even at levels just above two drinks per day, is a public health problem, but identifying patients with this potentially unhealthy drinking is hindered by the lack of tests. Several blood tests, such as those testing for gamma-glutamyl transpeptidase (GGT) or mean corpuscular volume (MCV), are among the commonly used markers to identify very heavy drinking, but combinations of these markers have rarely been tested in lighter drinkers. We examined the relationship between alcohol drinking and the levels of these markers in a national population-based study composed primarily of lighter drinkers. **Method:** Data were analyzed from 8,708 adult participants in the third U.S. National Health and Nutrition Examination Survey after excluding subjects with iron overload; with hepatitis B and C; who were pregnant; and who were taking prescription drugs such as phenytoin (Dilantin), barbiturates, and hydroxyurea (Droxia and Hydrea). The relationship between the amount of alcohol drinking and GGT, aspartate aminotransferase:alanine aminotransferase ratio, MCV of erythrocytes, and apolipoprotein A1 and B were analyzed and adjusted for potential liver injury risk factors. **Results:** The prevalence of unhealthy alcohol drinking (defined as consumption of more than two standard drinks per day) was 6.7%. Heavier drinkers tended to be younger and reported an average of 4.2 drinks per day. When tested alone or in combination, the sensitivity and positive predictive values for these blood tests were too low to be clinically useful in identifying the subjects in the heavier drinking category. **Conclusions:** In this large, national, population-based study, the markers of heavy drinking studied here, either alone or in combination, did not appear to be useful in identifying unhealthy drinking. More work is needed to find the novel marker(s) associated with risky alcohol drinking. (*J. Stud. Alcohol Drugs, 71,* 249-252, 2010)

UNHEALTY DRINKING (e.g., more than two standard drinks per day) is a major public health problem in the United States and worldwide (Serdula et al., 2004). However, the identification of patients with these problems is hindered by the lack of a sufficiently sensitive and specific screening test (Hannuksela et al., 2007). To date, face-to-face interviews and questionnaires such as CAGE and the Alcohol Use Disorders Identification Test are being used in clinical practice to determine the status of alcohol drinking in particular patients (Berks and McCormick, 2008; Bradley et al., 2007). However, heavier drinkers often underestimate their consumption.

For very heavy drinkers, who are likely to have alcohol dependence, some blood tests appear to be useful. The plasma levels of enzymes expressed in the liver—such as gamma-glutamyl transpeptidase (GGT), the aspartate aminotransferase (AST):alanine aminotransferase (ALT) ratio, and the mean corpuscular volume (MCV) of erythrocytes—are among the commonly used markers to identify chronic alcohol use (Hannuksela et al., 2007). Alcohol consumption also affects the levels of apolipoprotein A1 and B (the two major protein components of high-density and low-density lipoprotein cholesterol; Volcik et al., 2008).

The current study evaluates whether these markers of very heavy drinking might be useful for identifying potentially harmful lower levels of alcohol intake. We used data from a population-based study to characterize the association between alcohol drinking and the levels of several serum markers (such as MCV, GGT, AST, ALT, and apolipoprotein A1 and B).

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Method

The data set that was used in this study was from the third U.S. National Health and Nutrition Examination Survey (NHANES III), which was conducted in the United States from 1988 through 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention. This study was approved by the Centers for Disease Control and Prevention Institutional Review Board and was undertaken with informed consent. The survey used complex, multistage, stratified, clustered samples of civilian, noninstitutionalized populations age 2 months and older to collect information about health and diet. A detailed description of the survey and its sampling procedures are available on the Centers for Disease Control and Prevention Web site.

Study cohorts and definition

Of the 18,162 subjects with physical examinations and laboratory assessments, we excluded those older than 20 years old (n = 1,132) and those with missing values: GGT (n = 381), MCV (n = 993), hepatitis B serologies or hepatitis C serology (n = 390), body mass index (n = 80), AST or ALT (n = 1,297), and drinking history (n = 1,255). We also excluded subjects with the following parameters known to interfere with MCV levels: those who were pregnant (n = 280) and those with low serum transferrin saturation (<15%), low serum folate (<3.4 ng/ml), low serum vitamin B_{12}, and serum creatinine greater than 2 mg/dl (n = 3,436). Because the levels of MCV and GGT are influenced by medications, we also cross-linked our study cohort with the prescription drug data set in NHANES III and excluded 210 subjects who were taking phenytoin (Dilantin), barbiturates, hydroxyurea (Droxia and Hydrea), and methotrexate (Trexall). Therefore, a total of 8,708 subjects constituted our study cohort.

The average alcohol consumption was calculated from responses to two survey queries regarding the number of days of drinking over the past 12 months and the number of drinks per drinking day. Current alcohol consumption was coded as zero (nondrinker), less than one, one to two, or more than two drinks per day. Risky alcohol consumption was defined as more than two standard drinks per day (Ruhl and Everhart, 2005; Zakhari and Li, 2007).

The analyses also included the following covariates: age, gender, race or ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American), body mass index, and smoking status. The latter was placed into four categories—(a) never smoker, (b) former, (c) current smoker (less than one pack

TABLE 1. Clinical characteristics of study samples stratified by alcohol drinking (N = 8,708)

	Alcohol consumption (drinks/day)					
Clinical characteristics	0 (n = 3,840)	<1 (n = 3,544)	1-2 (n = 732)	>2 (n = 592)	p	Effect size[a]
Age, in years, *M* (*SE*)	50.5 (0.6)	42.4 (0.6)	42.3 (1.1)	41.4 (1.1)	<.001	.8
Gender, male, %	32	44	12	12	<.001	–
Ethnicity, %						
Non-Hispanic White	42	42	9	7	<.001	–
Non-Hispanic Black	55	31	8	6		
Mexican-American	65	28	3	4		
BMI, kg/m2, *M* (*SE*)	26.9 (0.2)	25.6 (0.2)	25.4 (0.2)	25.9 (0.3)	<.001	.5
Alcohol, drinks/day, *M* (*SE*)	0	0.4 (0.1)	1.5 (0.1)	4.2 (0.2)	<.001	.9
Cigarette smoking, never, %	52	39	5	4	<.001	–
Serum ALT activity, U/L						
M (*SE*)	17.4 (0.5)	17.2 (0.5)	18.3 (0.8)	22.2 (0.9)	<.001	.9
% elevated	6	4	6	10.4		
Serum AST activity, U/L						
M (*SE*)	21.5 (0.2)	20.8 (0.2)	22.6 (0.7)	25.2 (0.7)	<.001	.9
% elevated	5.4	3.3	6.1	9.7		
AST:ALT ratio						
M (*SE*)	1.5 (0.1)	1.4 (0.1)	1.5 (0.1)	1.3 (0.1)	<.001	–
% elevated	16.6	12.8	16.6	8.2		
MCV, Fl						
M (*SE*)	89.9 (0.2)	90.2 (0.1)	91.5 (0.3)	92.3 (0.4)	<.001	.9
% elevated	1.3	1.3	4.3	5.6		
GGT, U/L						
M (*SE*)	27.8 (0.9)	26.0 (0.8)	34.5 (2.1)	47.1 (3.4)	<.001	.9
% elevated	14.8	11.1	16.3	23.7		
Serum apolipoprotein A1, mg/dl,						
M (*SE*)	143.4 (1.1)	144.8 (1.0)	150.7 (3.2)	151.8 (2.2)	<.001	.8
Serum apolipoprotein B, mg/dl						
M (*SE*)	108.8 (1.4)	103.1 (0.9)	101.5 (1.9)	101.8 (2.2)	<.001	.9

Notes: BMI = body mass index; ALT = alanine aminotransferase; AST = aspartate aminotransferase; MCV = mean corpuscular volume; GGT = gamma-glutamyl transpeptidase. [a]Effect size was calculated by comparing the means of the variable of interest between those who drank more than two versus two or fewer drinks/day.

per day), and (d) current smoker (one or more packs per day)—based on three questions: "Have you smoked 100+ cigarettes in your life?" "Do you smoke cigarettes now?" and "How many cigarettes do you smoke per day?"

Laboratory measurements

As described in detail elsewhere (National Center for Health Statistics, 1995) venous blood samples were immediately centrifuged and shipped weekly at -20 °C to a central laboratory. In brief, serum ALT, AST, and GGT concentrations were assayed using a Hitachi 737 Analyzer (Boehringer-Mannheim Diagnostics, Indianapolis, IN), and normal values were defined as ALT equaling 40 U/L or less for men, 31 U/L or less for women; AST equaling 37 U/L or less for men, 31 U/L or less for women; GGT equaling 51 U/L or less for men, 33 U/L or less for women; and MCV (using a quantitative, automated hematology analyzer) equaling 100 fl or less. Apolipoprotein A1 and B results were measured using three different methods at different times (from 1988 to 1991), including radial immunodiffusion, rate immunonephelometry, and the World Health Organization-International Federation of Clinical Chemistry and Laboratory Medicine (WHO-IFCC), with results using the radial immunodiffusion and immunonephelometry methods adjusted to the WHO-IFCC method.

Statistical analysis

Comparisons among groups were made using analysis of variance for continuous variables and chi-square for the categorical variables. To determine the strength of the relationship between the variables, effect size was calculated using Cohen's method. Effect size greater than 0.5 was considered as large difference effect. Univariate and multivariate logistic regression analyses as well as weight-adjusted discriminant analysis were conducted to explore serum markers that are independently associated with significant alcohol consumption. Sensitivity, specificity, positive predictive value, and negative predictive value of each marker were reported.

Results

Demographic and clinical characteristics of the study samples

The sample consisted of 8,708 participants, whose demographic and clinical characteristics are shown in Table 1. There was no difference in demography between studied participants (n = 8,708) and those who were excluded (n = 9,454). As shown in Table 1, the 6.8% who reported intake of more than two alcoholic drinks per day were younger than those who reported no alcohol consumption during the past 12 months.

Performance of each diagnostic test regarding alcohol consumption

The prevalence of abnormal ALT and AST levels increased significantly from zero to greater than two drinks per day, as did MCV, GGT, and apolipoprotein A1 levels. However, the AST:ALT ratios demonstrated no such increases (in fact, decreases were observed), and apolipoprotein B values also decreased across drinking levels (Table 1). In the multivariate analyses controlling for potential confounders (e.g., body mass index and smoking history), only MCV, GGT, and apolipoprotein A1 were associated with significant alcohol consumption.

Subsequent sensitivity analysis and combination models were carried out to determine the performance of each test and the combined variables to predict risky alcohol consumption. As shown in Table 2, when tested alone or in combination, the sensitivity and positive predictive values for these blood tests were too low to be clinically useful in identifying the subjects in the heavier drinking category.

Discussion

In this large, national, U.S. population-based study, we found little support for usefulness of blood tests usually used as markers for very heavy drinking in detecting differences

Table 2. Sensitivity analysis and performance of each and combined diagnostic tests to predict significant alcohol consumption

Tests	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %
MCV	4.7	98.7	20.2	93.5
GGT	23.7	86.7	11.1	94.2
Apolipoprotein A1	46.7	59.5	8.6	93.2
MCV + GGT	1.59	99.8	33.8	93.5
MCV + apolipoprotein A1	4.3	99.1	28.3	92.7
GGT + apolipoprotein A1	19.0	95.3	24.8	93.5
MCV + GGT + apolopiprotein A1	2.7	99.95	82.7	92.6

MCV = mean corpuscular volume; GGT = gamma-glutamyl transpeptidase.

between zero and greater than two drinks per day. The sensitivities and positive predictive values indicate these tests are likely to have limited value in identifying nonalcoholic patients with unhealthy drinking in clinical settings.

It is important to keep the limitations of this brief report in mind. First, the cross-sectional design in NHANES does not enable us to address potential temporal associations between significant alcohol consumption and the variables of interest. Second, all information on drinking status is from self-reports without corroboration. Given the lack of routine biochemical tests to detect unhealthy drinking in the modest range reported here, there is a need to search for new markers of such alcohol consumption.

References

Berks, J., & McCormick, R. (2008). Screening for alcohol misuse in elderly primary care patients: A systematic literature review. *International Psychogeriatrics, 20,* 1090-1103.

Bradley, K. A., DeBenedetti, A. F., Volk, R. J., Williams, E. C., Frank, D., & Kivlahan, D. R. (2007). AUDIT-C as a brief screen for alcohol misuse in primary care. *Alcoholism: Clinical and Experimental Research, 31,* 1208-1217.

Hannuksela, M. L., Liisanantti, M. K., Nissinen, A. E., & Savolainen, M. J. (2007). Biochemical markers of alcoholism. *Clinical Chemistry and Laboratory Medicine, 45,* 953-961.

National Center for Health Statistics. (1995). Plan and operation of the third National Health and Nutrition Examination Survey, 1988-1994. Hyattsville, MD: Author.

Ruhl, C. E., & Everhart, J. E. (2005). Joint effects of body weight and alcohol on elevated serum alanine aminotransferase in the United States population. *Clinical Gastroenterology and Hepatology, 3,* 1260-1268.

Serdula, M. K., Brewer, R. D., Gillespie, C., Denny, C. H., & Mokdad, A. (2004). Trends in alcohol use and binge drinking, 1985-1999: Results of a multi-state survey. *American Journal of Preventive Medicine, 26,* 294-298.

Volcik, K. A., Ballantyne, C. M., Fuchs, F. D., Sharrett, A. R., & Boerwinkle, E. (2008). Relationship of alcohol consumption and type of alcoholic beverage consumed with plasma lipid levels: Differences between whites and African Americans of the ARIC study. *Annals of Epidemiology, 18,* 101-107.

Zakhari, S., & Li, T.-K. (2007). Determinants of alcohol use and abuse: Impact of quantity and frequency patterns on liver disease. *Hepatology, 46,* 2032-2039.