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Biological Markers of Alcohol Consumption in Nondrinkers, Drinkers, and Alcohol-Dependent Brazilian Patients

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Background: The purpose of this study was to compare the sensitivity and specificity of some new and traditional biological markers and indicators of health among Brazilian nondrinkers, drinkers, and alcohol-dependent patients.

Material and Methods: We evaluated 130 nondrinkers, 167 drinkers, and 183 alcohol-dependent drinkers from Brazil who participated in the WHO/ISBRA Study on State and Trait Markers of Alcohol Use and Dependence. A standardized WHO/ISBRA Interview Schedule provided background information on the subjects' characteristics including reported health problems and alcohol consumption. Blood samples were analyzed for aspartate aminotransferase (AST), carbohydrate deficient transferrin (CDT), γ-glutamyltransferase (GGT), blood alcohol levels (BAL), and platelet adenylate cyclase activity (basal levels [AC] and levels after stimulation with Gpp(NH)p, cesium fluoride, and forskolin).

Results: The alcohol-dependent drinkers presented higher levels of AST, GGT, AC, CDT, and BAL than the nondrinkers and drinkers, whose levels were similar. Sex differences in the sensitivity of CDT and AC were found. The alcohol-dependent women presented a lower prevalence of abnormal values of CDT and Gpp(NH)p-stimulated AC than the alcohol-dependent men, despite the fact that they presented similar alcohol consumption levels. The alcohol-dependent drinkers presented a higher prevalence of clinical disorders than the nondrinkers and drinkers. The drinkers and alcohol-dependent patients presented significantly higher rates of gastritis than the nondrinkers.

Conclusions: Sex differences in the sensitivity of CDT and AC suggest that these markers are not as sensitive at detecting excessive alcohol use in women as they are in men. If data from this Brazilian sample are compared with those reported for international samples, relevant differences are detected, which suggests that genetic and cultural differences should be considered in the selection of biological markers of heavy alcohol consumption.

Key Words: Alcohol, Aspartate Aminotransferase, γ-Glutamyltransferase, Adenylate Cyclase Activity, Carbohydrate-Deficient Transferrin.

THE MAIN OBJECTIVE of using biological markers of alcohol consumption is to improve the objectivity of both the diagnosis of alcoholism and the screening of people at risk of developing alcoholism, because some individuals tend to deny their consumption. Some markers, such as the levels of activity of the platelet enzymes monoamine oxidase and adenylyl cyclase (AC), are genetically determined and have been proposed as "trait" markers, because they are often lower in alcohol-dependent individuals, even after long periods of abstinence (Anthenelli and Tabakoff, 1995; Farren and Tipton, 1999; Menninger et al., 2000), and are not affected by alcohol consumption changes. Other traditionally used laboratory tests are considered "state markers" (Helander et al., 1996, 1997; Monteiro and Masur, 1987; Musshoff and Daldrup,1998) because they change as consumption changes and are therefore useful for following treatment and also can be used to provide feedback to patients (Monteiro and Masur, 1985, 1986).

Although some lab tests such as γ-glutamyltransferase (GGT), carbohydrate-deficient transferrin (CDT), and aspartate aminotransferase (AST) have been used as markers of excessive alcohol consumption or alcohol-related liver damage, they do not always present high levels of specificity

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because most of them also are altered by hepatic disorders not related to alcohol consumption (Conigrave et al., 2000; Huseby et al., 1997a,b; Lesch et al., 1996; Musshoff and Daldrup, 1998; Stowell et al., 1997; Wetterling et al., 1998). Furthermore, the sensitivity and specificity of these tests have been shown to be highly variable depending on factors such as sex, age, and genetic characteristics (Anton and Moak, 1994; Mumenthaler et al., 1999; Mundle et al., 1999, 2000; Potter, 1994)

Some studies have suggested that CDT presents higher clinical utility than GGT in identifying recent alcohol consumption (Huseby et al., 1997a; Schmidt et al., 1997). CDT is considered a good marker of acute and chronic alcohol consumption with specificity values around 90% (Bell et al., 1994). Although its reported sensitivity values vary from 69% to 100% in populations with daily alcohol consumption over 50 g (Bell et al., 1994; Potter, 1994), some authors have suggested that CDT presents low sensitivity in women and young drinkers (Anton et al., 1998; Gronbaek et al., 1995; La Grange et al., 1995, Nystrom et al., 1992). Similar conclusions were reached by Bräthen et al. (2001), who reported that the accuracy of CDT for the detection of alcohol abuse, in a sample of 484 patients with neurological disorders, was generally low, particularly for women. Although there are some data on the performance of GGT, AST, and alanine aminotransferase as biological markers in Brazilian samples of alcohol-dependent individuals (Macieira et al., 1993; Monteiro and Masur, 1985, 1986, 1987; Rieck and Formigoni, 1994), we haven't found any reference to the performance of CDT in Brazilians.

Among more recently developed biological markers of alcoholism, one of the most consistent trait markers is the response to stimulation of AC in platelets and lymphocytes. This enzyme is activated by hormones and neurotransmitters to increase the production of adenosine 3':5'-cyclic monophosphate. Tabakoff et al. (1988) reported that although baseline AC levels are the same in alcoholic-dependent individuals and controls, there is a low responsiveness to stimulation in alcohol-dependent individuals, which persists even after 12 months of abstinence. Low platelet AC activity has been proposed as a trait marker for predisposition to alcohol dependence (Tabakoff and Hoffman, 1998). To the best of our knowledge, there are no data about the performance of this marker in Brazilians.

The WHO/ISBRA Study on State and Trait Markers of Alcohol Use and Dependence was a multinational investigation established in 1988 that involved investigators from seven countries: Australia, Brazil, Canada, Finland, Japan, Sweden, and the United States. It was designed to aid in the development of biological screening tools (state markers) that can, with good sensitivity and specificity, identify problem drinkers. To attain this goal, information needs to be available on an individual's drinking history and habits and related factors. A detailed instrument has been developed to obtain this information. The second goal of the study was to begin to develop diagnostic "trait markers" that provide biological information on genetically determined predisposing and protective factors in the development of alcoholism (Helander at al., 1997).

The main objective of this article was to analyze the specificity and sensitivity of GGT, CDT, AST, AC, and blood alcohol level (BAL) in male and female Brazilian drinkers, classified into three groups according to their reported alcohol consumption levels. The secondary objective was to analyze the prevalence in the same groups of reported health problems that could be related to alcohol consumption.

METHODS

Subjects

Subjects were 480 Brazilians (271 men and 209 women) between the ages of 18 and 60. The subjects were classified into three categories: nondrinkers, drinkers, and alcohol-dependent drinkers, based on their responses to an extensive interview (Tabakoff and Dongier, 1996) about their alcohol consumption habits. In classifying the subjects, we used the following criteria:

Nondrinkers (n = 130): Individuals who reported drinking alcohol on at most six occasions per year with a consumption of no more than 15 g of ethanol on each occasion.

Drinkers (n = 167): Individuals who reported alcohol consumption during the last month of no more than 210 g/week for men or 140 g/week for women and who had not sought treatment or fulfilled the criteria for alcohol dependence at any point during the last year.

Alcohol-dependent patients (n = 187): Individuals who reported alcohol consumption over 210 g/week for men or 140 g/week for women and fulfilled the DSM-III-R, DSM-IV, or ICD-10 criteria for alcohol dependence or had done so during the last year.

Most of the alcohol-dependent patients were recruited from programs that specialized in substance abuse/dependence treatment. The nondependent subjects were recruited from a nonhospital environment in response to research solicitations. Exclusion criteria included major medical or psychiatric disorders, intravenous drug abuse, and recent treatment with dissulfiram, tolbutamide, or other aldehyde dehydrogenase inhibitors.

Blood Samples and Biochemical Assays

Blood samples were collected at the time of the interview via the standard venipuncture technique into vacutainers that contained EDTA for preparation of plasma and platelets. After separation of blood cells, plasma, and serum, as described by Helander et al. (1997) and Menninger et al. (2000), the material was shipped in dry ice to the Helsinski Coordinating Center and, in turn, to the respective assay centers. AC activity was assayed by the Department of Pharmacology, University of Colorado Health Sciences Center, Denver, Colorado. GGT, BAL, and AST activities were assayed at the laboratories of ALKO and KTL, Helsinski, Finland. CDT was assayed at the Alcohol Diagnostics Laboratory at St. Gorans Hospital, Stockholm, Sweden. The specific procedures of each analysis are described in Menninger et al. (2000).

Statistical Analysis

Analyses of variance, followed, when necessary, by Tukey's honestly significant difference statistic, were used to compare mean values across the three drinking category groups. Different analyses were performed for the men and women. Student's t test was used to compare the means across the men and women from the same drinking category. The χ^2 test was used to compare categorical variables across two or more groups. A 5% level of significance was used for all the comparisons.

Table 1. Social and Demographic Characteristics of the Nondrinkers, Drinkers, and Alcohol-Dependent Brazilian Patients (Percentage of People in Each Drinking Group)

	Drinker category		
	Nondrinkers (n = 130)	Drinkers (n = 167)	Alcohol-dependent drinkers (n = 183)
Age in years (mean ± SD)			
Male	31 ± 9*	36 ± 12	38 ± 10
Female	38 ± 14	37 ± 12	38 ± 12
Sex (% of category)			
Male	42	50	73**
Female	58	50	27
Race (% of category)			
White	72	78	62
Black	14	9	20
Asian	5	4	2
Others	9	9	16
Education (% of category)			
≤8 years of schooling	40	31	66**
High school	28	24	21
College/university	32	45	13

* Males differ from females of the same drinker category, Student's t test $p < 0.05$;
** differs from the other drinker category groups χ^2, $p < 0.05$.

To evaluate the validity of the biological markers as screening tests, the nondrinkers were considered the reference (control) group. Sensitivity, specificity, and predictive values were calculated considering three different target conditions to be detected: (a) non-alcohol-dependent drinkers; (b) drinkers including alcohol-dependent individuals; and (c) only alcohol-dependent drinkers.

Ethical Considerations

The study was approved by the Ethics Committee for Medical Research of the Federal University of São Paulo, Brazil. All subjects signed an informed consent form before participation in the study.

RESULTS

Demographic Characteristics of the Subjects

The demographic characteristics of the subjects according to the alcohol consumption categories and sex are presented in Table 1. The percentage of women was smaller in the alcohol-dependent group because there were only a small number of women under treatment in the programs from which this group was recruited. The drinking groups were similar regarding age, but women were older than men in the nondrinkers group. The men from the alcohol-dependent group were more likely to be less educated than those from the nondrinkers and drinkers groups.

Alcohol Consumption and Dependence

Table 2 shows the alcohol consumption characteristics of the groups. Of those currently classified as drinkers, 12% of the men and 5% of the women fulfilled the DSM-III-R criteria for alcohol dependence at some point in their lifetime. None of the nondrinkers had ever fulfilled these criteria in their lifetime.

The mean alcohol consumption of the alcohol-dependent patients was 144 g/day for women and 149 g/day for men. In the drinkers group, the means were 4.3 g/day for women and 8.4 g/day for men. Most of the alcohol-dependent drinkers reported an intake higher than 40 g/day, whereas just 2% of the men classified as drinkers reported such a high level of consumption.

Biological Markers

Table 3 shows the mean values of GGT, AST, CDT, BAL, and AC in the three groups. The mean values of AST, GGT, and CDT were significantly higher in the alcohol-dependent group than in the others.

Nondrinkers and drinkers of the same sex presented similar levels of AST and CDT. Women from the nondrinkers and drinkers groups presented higher values of CDT than the men from the same groups. However, the alcohol-dependent women presented lower levels of CDT than the alcohol-dependent men.

The GGT levels of the alcohol-dependent men were twice as high as those presented by the alcohol-dependent women. Mundle et al. (2000) reported lower sensitivity of GGT as an alcohol dependence marker in women. Similar data were found in the drinkers group, in which the GGT values of the men were about 1.5 times higher than those found in the women. This could be partially attributed to the difference in alcohol daily consumption, because the female drinkers reported lower consumption. However, in the nondrinkers group, women also presented higher levels of CDT, which suggested that these differences may not be related only to the different levels of alcohol consumption.

The levels of AC without stimulation (basal), as well as after stimulation with cesium fluoride (CSF) or forskolin (FOR), were similar among the groups, but after stimulation by Gpp(NH)p they were significantly higher in the men from the alcohol-dependent group.

BALs were higher in the alcohol-dependent men than in the women from the same group, which indicated that men

Table 2. Alcohol Consumption, Abuse, and Dependence According to Alcohol Consumption Group and Sex (Percentage of People in Each Drinking Group)

	Nondrinkers	Drinkers	Alcohol-dependent drinkers
Average alcohol consumption (g/day) during last month (mean ± SD)			
Male	0	8.4 ± 7.6	149 ± 103
Female	0	4.3 ± 4.5	144 ± 82
Alcohol consumption (last 30 days) (% of category)			
< 20 g/day			
Male	100	86	0
Female	100	100	0
20–39 g/day			
Male	0	12	2
Female	0	0	6
40–79 g/day			
Male	0	2	29
Female	0	0	24
≥80 g/day			
Male	0	0	69
Female	0	0	70
Alcohol abuse (lifetime) %			
Male	0	20.0	96.0
Female	0	1.2	86.0
Alcohol dependence (lifetime) %			
Male	0	12.0	100.0
Female	0	5.0	100.0

Table 3. Biochemical Markers in Nondrinkers, Drinkers, and Alcohol-Dependent Drinkers

	Nondrinkers		Drinkers		Alcohol-dependent drinkers		
	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	ANOVA
AC basal							
Male	15 ± 8	54	14 ± 8	84	15 ± 6	133	NS
Female	14 ± 12	76	13 ± 6	83	14 ± 5	50	NS
AC GPP							
Male	67 ± 27	31	59 ± 35	57	75 ± 27[c]	88	$p = 0.009$
Female	59 ± 29	58	54 ± 27	63	67 ± 28	27	NS
AC CSF							
Male	105 ± 24	33	119 ± 32[a]	65	110 ± 34	96	NS
Female	105 ± 28	59	109 ± 27	65	104 ± 31	33	NS
AC FOR							
Male	305 ± 99[a]	31	304 ± 123	59	297 ± 88	88	NS
Female	260 ± 77	58	269 ± 80	64	292 ± 82	27	NS
AST							
Male	29 ± 11[a]	50	29 ± 9	80	89 ± 161[bc]	133	$p < 0.0001$
Female	24 ± 6	76	28 ± 25	80	48 ± 48[bc]	46	$p < 0.0001$
GGT							
Male	36 ± 32[a]	50	50 ± 79	80	218 ± 428[bc]	133	$p < 0.0001$
Female	23 ± 14	76	36 ± 76	80	101 ± 128[bc]	46	$p < 0.0001$
CDT							
Male	13 ± 3[a]	50	14 ± 4[a]	80	33 ± 23[abc]	126	$p < 0.0001$
Female	17 ± 5	76	16 ± 5	81	24 ± 10[bc]	48	$p < 0.0001$
BAL							
Male	0.02 ± 0.15	43	0.03 ± 0.25[b]	79	2.47 ± 7.78[ac]	108	$p < 0.01$
Female	0.20 ± 1.13	75	0.40 ± 2.40	82	0.07 ± 0.25	45	NS

CDT, GGT, and ASAT values are expressed as units/liter, ethanol in μmol/liter, and platelet adenylyl cyclase activity in pmol cAMP/mg protein/min. Levels considered elevated: ethanol, >0; CDT, >27 for women and >20 for men; GGT, >50 for women and >80 for men; AST, >35 for women and >50 for men.

Comparisons among the groups were made using ANOVA, followed, when necessary, by Tukey's test.

[a] Differs from women with the same level of alcohol consumption ($p < 0.05$, Student's *t* test);

[b] Differs from nondrinkers ($p < 0.05$, Tukey's test);

[c] Differs from drinkers ($p < 0.05$, Tukey's test).

presented a more recent alcohol consumption or that women presented lower metabolism (Baraona et al., 2001).

Table 4 shows the psychometric properties of CDT, GGT, AST, and BAL if used in the detection of nondependent drinkers, drinkers including alcohol-dependent subjects, and alcohol-dependent subjects. In the three analyses, the nondrinkers group was used as reference (control). Significant variations in sensitivity were found across the three conditions. For men, CDT presented the best sensitivity, varying from 10% in the detection of non-alcohol-dependent drinkers to 64.3% in the detection of alcohol-dependent drinkers. For women, GGT presented

Table 4. Sensitivity, Specificity, Positive Predictive Value (PV+) and Negative Predictive Value (PV−) of elevated CDT, GGT, AST, and EtOH levels, according to Sex.

	Men				Women			
	Sensitivity	Specificity	PV+	PV−	Sensitivity	Specificity	PV+	PV−
In detection of non-alcohol-dependent drinkers								
CDT	10.0	100.0	100.0	41.0	17.3	96.2	82.4	53.1
GGT	7.5	98.0	85.7	39.8	11.3	96.1	75.0	50.7
AST	5.0	94.0	57.1	38.2	11.3	94.7	69.2	50.3
BAL	2.5	97.7	66.7	35.3	7.3	94.7	60.0	48.3
In detection of drinkers, including alcohol-dependent patients								
CDT	43.2	100.0	100.0	29.9	25.6	96.2	82.4	53.1
GGT	35.7	98.0	98.7	26.3	25.4	96.1	91.4	43.7
AST	29.1	94.0	95.4	23.7	22.2	94.7	87.5	42.4
BAL	9.6	97.7	94.7	19.9	7.1	94.7	69.2	37.6
In detection of alcohol-dependent drinkers								
CDT	64.3	100.0	100.0	52.6	39.6	96.2	86.4	72.4
GGT	52.6	98.0	98.6	43.8	50.0	96.1	88.5	76.0
AST	43.6	94.0	95.1	38.5	41.3	94.7	82.6	72.7
BAL	14.8	97.7	94.1	31.3	6.7	94.7	42.9	62.8

Levels considered elevated: ethanol; >0; CDT: >27 for women and >20 for men; GGT: >50 for women and >80 for men; AST: >35 for women and >50 for men.

the best sensitivity, varying from 11.3% in the detection of non-alcohol-dependent drinkers to 50% in the detection of alcohol-dependent drinkers. BAL presented the worst sensitivity value in the detection of alcohol-dependent drinkers (14.8% for men and 6.7% for women). These four biological markers showed high specificity values, from 94.7% to 100%. Elevated CDT presented the highest positive predictive value (PPV) in the detection of alcohol-dependent men (100%), whereas for detecting alcohol-dependent women, GGT presented the highest PPV (88.5%).

Reported Medical Disorders

Table 5 shows the percentages of reported medical disorders in the three groups. The alcohol-dependent group presented higher incidences of enlarged liver, cirrhosis, pancreatitis, gastritis, tuberculosis, convulsions, and high blood pressure compared with the nondrinkers or the drinkers. A significantly higher percentage of gastritis (8.5% for women and 19% for men, $\chi^2 = 12, p < 0.05$) was observed in the drinkers group when compared with the nondrinkers. Blood pressure levels were higher in the men of the alcohol-dependent group (34.6%) than in the drinkers (16%) or nondrinkers (13%). For the women, these levels were higher in the nondrinkers (22%) than in the drinkers (9.6%) and alcohol-dependent drinkers (3.6%).

DISCUSSION

The usefulness of biological markers in detecting alcoholism varies depending on sex. In general, these markers were less sensitive in women than in men. If our data are compared with those reported in the literature, some differences are detected, which suggests that genetic and cultural differences should be considered in the selection of biological markers of heavy alcohol consumption. Compared with data from a German sample reported by Mundle et al. (2000), the sensitivity of GGT in detecting alcohol dependence in our Brazilian sample was lower in both the men (52.8% in Brazil vs. 68% in Germany) and women (50% vs. 57%). On the other hand, the sensitivity of CDT was higher in Brazilian men (64.3% vs. 46%) but lower in women (39.6% vs. 49%). In general, some evidence indicates that the performance of the tests can be improved with combined CDT and GGT (Helander et al., 1996; Salaspuro, 1999; Sillanaukee et al., 2000b), but in some cases, as in pregnant women, the sensitivity of GGT is better than that of CDT (Sarkola et al., 2000).

In our sample, the alcohol-dependent women presented lower rates of abnormal values of CDT and BAL than the alcohol-dependent men, despite the fact that they had similar alcohol consumption levels, which limited their utility as biological markers of heavy alcohol consumption in Brazilian women. Despite these lower rates of abnormal values of CDT, the non-alcohol-dependent women drinkers presented higher mean values than the men of the same category. These data confirm a number of studies in the literature that also have reported higher CDT levels in non-alcohol-dependent and abstinent females than in males with the same alcohol consumption profile (Stibler, 1991; Stibler et al., 1991; Nystrom et al.,1992). Sillanaukee et al. (2000a) reported that different hormonal status has opposite effects on CDT and GGT. Women who are close to late menopause have levels of CDT and GGT nearer to the values of men.

CDT, GGT, and AST presented good specificity levels for both men and women. Considering the present data, CDT was the best biological marker for screening alcoholism among men (64.3% sensitivity, 100% specificity, and 100% PPV), whereas GGT presented the best indicator for women (50% sensitivity, 96.1% specificity, and 88.5% PPV).

Nilssen et al. (1990), who studied factors that interfere with GGT, pointed out that many factors such as dietary components (coffee), medications (oral contraceptives), and physical activity may alter its values. Considering that

Table 5. Reported Medical Problems by Drinker Category (Percentage of Patients)

Reported disorders	Drinker category: Nondrinkers (N)	Drinkers (D)	Alcohol-dependent drinkers (A)	Comparison among groups (χ^2 test)
Enlarged liver	0.1	1.8	14.8	33.8 $p \leq 0.001$ (N = D) ≠ A
Male	0.0	2.4	14.4	16.0 $p \leq 0.001$ (N = D) ≠ A
Female	1.3	1.2	16.0	17.9 $p < 0.001$ (N = D) ≠ A
Hepatitis	5.0	4.2	9.3	NS
Male	3.7	4.8	10.5	NS
Female	6.6	3.6	6.0	NS
Stomach, duodenal ulcer	3.0	8.4	9.3	NS
Male	3.7	10.7	10.5	NS
Female	2.6	6.0	6.0	NS
Cirrhosis of liver	0.0	0.0	3.8	11.5 $p \leq 0.003$ (N = D) ≠ A
Male	0.0	0.0	4.5	6.37 $p \leq 0.001$ (N = D) ≠ A
Female	0.0	0.0	2.0	NS
Kidney disease	8.5	15.6	11.5	NS
Male	5.6	11.9	9.8	NS
Female	10.5	19.3	16.0	NS
Pancreatitis	0.0	1.8	4.9	7.8 $p \leq 0.02$ (N = D) ≠ A
Male	0.0	2.5	6.0	NS
Female	0.0	1.2	2.0	NS
Gastritis	2.3	13.8	15.3	14.5 $p \leq 0.001$ N ≠ (D = A)
Male	1.8	19.0	15.8	8.7 $p \leq 0.05$ N ≠ (D = A)
Female	2.6	8.4	14.0	5.6 $p < 0.06$ NS
Thyroid disease	7.9	4.2	2.2	NS
Male	0.0	2.4	0.7	NS
Female	11.8	6.1	6.0	NS
Diabetes	4.6	2.4	4.9	NS
Male	3.7	2.4	4.5	NS
Female	5.3	2.4	6.0	NS
Hyperlipidemia	14.6	15.0	8.2	NS
Male	9.3	13.1	9.0	NS
Female	18.4	16.9	6.0	NS
Tuberculosis	0.1	1.8	6.6	9.8 $p \leq 0.007$ (N = D) ≠ A
Male	1.9	1.2	7.6	5.9 $p < 0.06$ NS
Female	0.0	2.4	4.0	NS
Vitamin deficiency/anemia	27.0	22.0	24.6	NS
Male	22.2	13.1	20.3	NS
Female	30.3	31.7	36.0	NS
Convulsions	4.6	2.4	26.2	56.1 $p \leq 0.00001$ (N = D) ≠ A
Male	3.7	1.2	29.3	38.3 $p \leq 0.00001$ (N = D) ≠ A
Female	5.3	3.6	18.0	10.1 $p < 0.01$ (N = D) ≠ A
Arthritis, osteoporosis	7.7	8.4	10.4	NS
Male	0.0	5.9	10.7	6.9 $p < 0.05$ (N = D), (D = A), (N ≠ A)
Female	13.2	11.0	10.0	NS
Emphysema, lung disease	10.0	12.6	18.0	NS
Male	9.3	16.7	17.3	NS
Female	10.5	8.5	20.0	NS
High blood pressure	18.5	13.2	35.0	25.5 $p \leq 0.0001$ (N = D) ≠ A
Male	13.0	16.7	34.6	13.9 $p < 0.001$ (N = D) ≠ A
Female	22.4	9.6	36.0	13.5 $p < 0.05$ (N = A) ≠ D
Heart disease	7.8	5.4	8.2	NS
Male	9.3	4.8	9.0	NS
Female	6.8	6.0	6.0	NS
Cancer	1.5	0.6	2.2	NS
Male	0.0	0.0	2.3	NS
Female	2.6	1.2	2.0	NS
Immune system problems	7.7	1.2	1.1	NS
Male	1.9	1.2	0.7	NS
Female	0.0	1.2	2.0	NS
Other medical problems	22.0	22.1	13.7	NS
Male	23.1	26.2	15.8	NS
Female	21.1	18.3	8.0	NS

Brazilians usually consume high amounts of coffee, this factor deserves further investigation.

Scouller et al. (2000) performed a systematic review and meta-analysis of studies on CDT and concluded that depending on the quality of CDT assays, CDT is not significantly better than GGT as a marker of excessive alcohol use and that more studies are needed.

Concerning AC as an indicator of alcohol dependence, no differences were found among the groups, either in their basal values or after stimulation with CSF or FOR, although a small but significant difference in the mean levels of AC activity after stimulation with CSF was detected between men and women from the non-alcohol-dependent group. After stimulation with Gpp(NH)p, AC activity levels differentiated alcohol-dependent patients from non-alcohol-dependent drinkers but not from nondrinkers. These data differ from those reported by Menninger et al. (2000), who worked with an Australian population. As was pointed out by these authors, many factors, among them recent alcohol consumption, influence AC activity values. Studies with larger samples are necessary to further investigate the utility of this biological marker.

There was a higher prevalence of clinical disorders among the alcohol-dependent individuals than the nondrinkers and drinkers, but, notably, the drinkers also presented a higher incidence of gastritis when compared with the nondrinkers. This suggests that although the non-alcohol-dependent drinkers did not differ from the nondrinkers in their mean levels of GGT, AST, and CDT, their alcohol consumption still may be considered a risk in relation to some medical disorders such as gastritis. In our sample, the non-alcohol-dependent drinkers reported an alcohol consumption between 8.4 ± 7.6 g/day (men) and 4.3 ± 4.5 g/day (women).

In summary, our data suggested that CDT, GGT, and AST are useful as biological markers of alcohol dependence in Brazilian patients, with CDT being more sensitive in men and GGT more sensitive in women.

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