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UNEXPECTED EFFECTS OF COFFEE CONSUMPTION ON LIVER ENZYMES

E. CASIGLIA*[1], P. SPOLAORE**, G. GINOCCHIO* and G.B. AMBROSIO*

Istituto di Medicina Clinica dell'Università di Padova - Clinica Medica 1 - Policlinico Universitario Via Giustiniani, 2 - 35126 Padova, Italy.

***Direzione Sanitaria e Divisione di Cardiologia dell'Ospedale di Castelfranco Veneto (Treviso), Italy.*

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The effects of regular daily coffee consumption on liver enzymes were studied in a large number of subjects from the general population. In coffee drinkers, liver enzymes (gamma-glutamyl transferase, alanine-amino transferase, and alkaline phosphatase) and serum bilirubin were lower than in non-coffee-drinking subjects or in those consuming less than 3 cups daily. The hypothesis proposed is that liver enzymes are a target for caffeine contained in coffee.

INTRODUCTION

Both the general (4) and haemodynamic (1, 3) chronic effects of coffee consumption have been studied. On the contrary, the effects of chronic daily coffee consumption on the liver has not been described to date.

In 2240 subjects (827 males and 1413 females), aged 65 years or over, from the 3088 elderly subjects of the general population of the Italian town of Castelfranco Veneto (Treviso) participating in the *CASTEL* Study (Cardiovascular Study in the Elderly), daily brewed Italian coffee consumption was taken into consideration relative to liver enzyme plasma levels.

SUBJECTS AND METHODS

The *CASTEL* study: This report is based on data from the Cardiovascular Study in the Elderly (*CASTEL*), an epidemiological prospective intervention trial carried out in Italy (2). The *CASTEL* cohort includes 2254 elderly men and women from the general population, followed for 7 years in order to evaluate the prevalence of hypertension in elderly people and their cardiovascular risk.

Design of the study: All subjects aged 65 years or over from the general population of Castelfranco Veneto (3088 subjects identified by the register's office) were asked to participate in the study; 2254 (73%) agreed and were enrolled in the period from 1983 to 1985. For the purpose of the present study, the results obtained in 2240 subjects were taken into consideration, while 14 cases in which data on coffee consumption or on liver enzymes were not available were rejected. Subjects were divided into *Class 1* (drinking less than 3 cups of coffee per day) and *class 2* (drinking 3 cups or more per day), and had comparable daily consumption of alcohol and cigarettes.

Data collection: The following parameters were recorded at the initial screening and at the final 7-year visit: clinical history, blood pressure taken following World Health Organization procedure specifications

[1] Corresponding author.

of a cuff of adequate dimensions and blood collection for *routine* analysis (2). Plasma levels of gamma-glutamyl transferase (GGT), alanine-amino transferase (ALT), alkaline phosphatase (ALP), and bilirubin were detected in a morning fasting blood sample.

A two-dimensional-guided monodimensional echocardiogram was also performed in 559 randomly chosen subjects using a *random numbers generation computer procedure.* End-diastolic diameter (LVEDD) and systolic diameter (LVSD) were measured (in mm) from short-axis view (parasternal), and long-axis views were also used when necessary. End-diastolic and systolic left ventricular volumes (LVEDV and LVSV, in ml) were calculated with the formula of Teicholz (6):

$$\text{volume} = \frac{7 \text{ x diameter}^3}{2.4 + \text{diameter}}$$

and left ventricle ejection fraction (EF, %) with the formula:

$$\text{EF} = 100 \text{ x } \frac{\text{SV}}{\text{LVEDV}}$$

where SV = LVEDD-LVSD is stroke volume (in ml). Cardiac out-put (CO, in l/min) was calculated by multiplying SV by heart rate, and cardiac index (CI, in l/[min. sm]) by dividing CO by body surface area (*BSA*, in sm) obtained with the formula of Du Bois and Du Bois (5):

$$\text{BSA} = \text{weight}^{0.425} \text{ x height}^{0.725} \text{ x } 71.84$$

Cut-off values: Cut-off «normal» values for AST, ALT, GGT and ALP were, respectively, 45 IU/l, 55 IU/l, 65 IU/l and 125 IU/l mg/dl.

Statistics: Statistics were performed using the Systat package. Pearson chi-square was employed in order to compare frequencies. Means were compared with analysis of variance (ANOVA) and the Tukey *post hoc* correction. A Bartlett's test was performed to compare class 1 with class 2. Correlation was performed using the Pearson correlation test with the Bonferroni correction. Multiple analysis of covariance (MANCOVA) and multiple regression were performed in order to evaluate the influence of each variable of liver function on the others; for these purposes, AST, ALT, GGT, and ALP were used as dependent variables in further steps. A p-value of less than 0.05 was considered significant.

RESULTS

Plasma levels of gamma-glutamyl transferase (GGT), alanine-amino transferase (ALT), and alkaline phosphatase (ALP) were lower in class 2 than in class 1 (-17%, -10.3% and -4.7% respectively); all differences, (except for bilirubin), were highly significant as determined with the Bartlett's test for homogeneity of group variance (Table 1). Bilirubin serum levels were also lower in class 2 than in 1 (-5.5%). The trend of AST, ALT, GGT, and ALP serum levels in relation to the daily number of cups of coffee are shown in Figure 1. MANCOVA demonstrated that the relationship between daily number of cups of coffee and serum enzyme levels was significant (F-ratio = 124.5, p = 0.0001 for AST; F-ratio = 59.7, p = 0.0001 for ALT; F-ratio = 58.9, p = 0.0001 for GGT; F-ratio = 730.7, p = 0.0001 for ALP).

Daily coffee consumption in cups per day inversely correlated with serum levels of GGT (r = -0.075, p = 0.0001), AST (r = -0.058, p = 0.006), ALT (r = -0.075, p = 0.0001), and ALP (r = -0.06, p = 0.001) (Fig. 2), and slightly with serum levels of bilirubin (r = - 0.043, p = 0.0410); GGT reduction directly correlated with the decrease of ALT (r = 0.404, p = 0.0001), ALP (r = 0.362, p = 0.0001), and bilirubin (r = 0.188, p = 0.0001). Serum alkaline phosphatase directly

TABLE 1. - Liver enzymes and bilirubin in 2240 elderly subjects drinking 3 cups of coffee per day (class 2) or less (class 1). Statistical analysis by means of Bartlett test.

Variable	Class 1 0-2 cups/day n = 1663	Class 2 ≥ 3 cups/day n = 577	Percent fall from class 1 to 2	p value
Coffee (cups/day)	1.45 ± 0.61	3.33 ± 0.87	-	0.0001
GGT (IU/l)	26.87 ± 27.95	22.30 ± 18.60	17.0%	0.0001
AST (IU/l)	16.30 ± 15.02	14.62 ± 12.47	10.3%	0.0160
ALP (IU/l)	143.8 ± 31.5	137.0 ± 44.9	4.7%	0.0060
bilirubin (mg/dl)	9.65 ± 7.86	9.12 ± 4.21	5.5%	0.1170

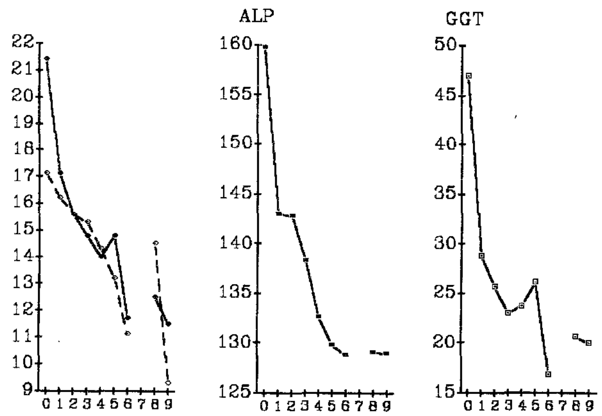

Figure 1. - Trend of serum levels of AST (solid line in left panel), ALT (dashed line in left panel), ALP (central panel) and GGT (right panel), in IU/l in relation to daily number of cups of coffee (in *abscissa*) among 2240 elderly subjects aged 65 years or over of the *CASTEL* cohort; no patient took 7 cups per day. *ANOVA:* F = 1.030, p = 0.413 for AST; F = 2.159, p = 0.028 for ALT; F = 5.68, p = 0.0001 for GGT; F = 2.90, p = 0.003 for ALP; *p* values vs non-coffee-drinkers obtained with the Tukey *post-hoc* test: *ALT:* 2 cups p = 0.029, 3 cups p = 0.012, *GGT:* 1 cup p = 0.0001, 2 cups p = 0.0001, 3 cups p = 0.0001, 5 cups: p = 0.0001; *ALP:* 1 cup p = 0.018, 2 cups p = 0.012, 3 cups p = 0.001, 4 cups p = 0.005. See text for *ANOCOVA*.

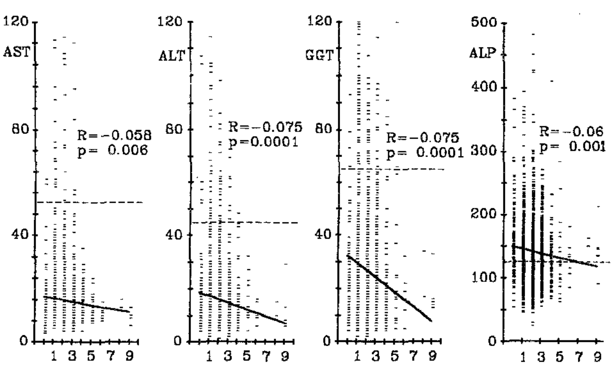

Figure 2. - Correlations between serum liver enzymes (ordinate, in IU/l) and daily coffee consumption (*abscissa*, in cups per day) among 2240 elderly subjects aged 65 years or over of the CASTEL cohort. Dashed lines indicate cut-off «normalcy» limits. *R.* is the Pearson regression coefficient.

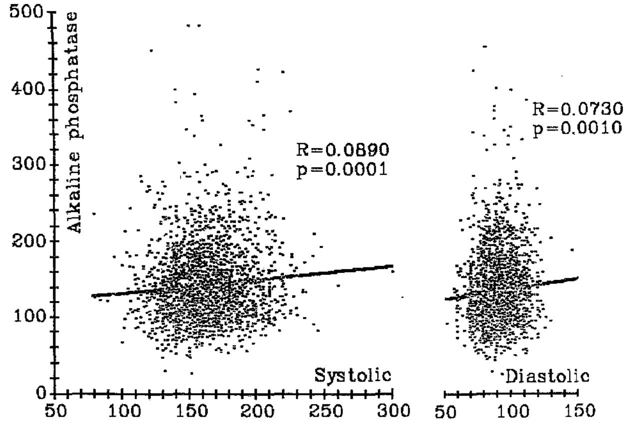

Figure 3. - Correlations between serum ALP levels (in IU/l) and blood pressure values (in mmHg) among 2240 elderly subjects aged 65 years or over of the CASTEL cohort. *R* is the Pearson regression coefficient.

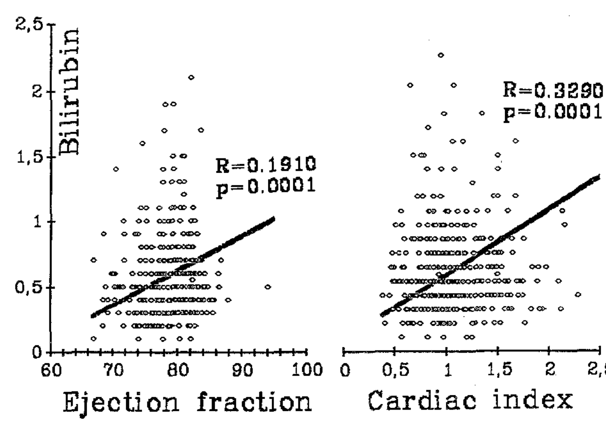

Figure 4. - Correlations between serum bilirubin level (in mg/dl) and two indexes of cardiac contractility (ejection fraction, %; cardiac index, in ml/[min. sm]) among the 559 elderly subjects aged 65 years or over from the CASTEL cohort who underwent echocardiogram. *R* is the Pearson regression coefficient.

correlated with both systolic (R = 0.089, p = 0.0001) and diastolic blood pressure (R = 0.073, p = 0.001) (Fig. 3). Serum bilirubin directly correlated with both ejection fraction (R = 0.191, p = 0.0001) and cardiac index (R = 0.329, p = 0.0001) among the 559 subjects in which echocardiogram was performed (Fig. 4). Multivariate regression analysis confirmed that the relation between daily coffee consumption and liver enzymes was significant also when age, smoking, and alcohol were taken into consideration (Table 2).

No correlation was found between daily coffee consumption and systolic blood pressure (R = -0.037, p = 0.079, NS), diastolic blood pressure (R = 0.009, p = 0.669, NS), EF (R = -0.028, p = 0.536, NS) and cardiac index (R = -0.028, p = 0.535, NS).

DISCUSSION

In our study serum liver enzymes were consistently lower in coffee drinkers than in non-coffee drinkers; the higher the daily number of cups of coffee, the lower the serum level of all liver enzymes and bilirubin. Figure 2 also shows that, in subjects consuming large amounts of coffee, serum AST, ALT, GGT and bilirubin were consistently below the «normal» values used in this study.

TABLE 2. - Multiple regression between liver enzyme plasma levels, age and other parameters among 2240 elderly subjects. *Coffee* is expressed as cups per day, *smoking* as cigarettes per day, *alcohol* as ml of ethanol per day, and age in years.

Dependent variable	Covariates	Coefficient	T	p	
AST	**coffee**	**-0.020**	**-2.488**	**0.013**	
	alcohol	0.056	5.246	0.0001	
	smoking	-0.004	-1.600	0.110	(NS)
	age	-0.021	-0.970	0.332	(NS)
ALT	**coffee**	**-1.331**	**-3.650**	**0.0001**	
	alcohol	0.237	0.491	0.630	(NS)
	smoking	-0.055	-0.540	0.589	(NS)
	age	-0.021	-0.970	0.332	(NS)
GGT	**coffee**	**-3.338**	**-4.266**	**0.0001**	
	alcohol	5.870	5.666	0.0001	
	smoking	0.339	1.539	0.124	(NS)
	age	0.081	0.505	0.613	(NS)
ALP	**coffee**	**-2.402**	**-2.417**	**0.016**	
	alcohol	-4.345	-3.303	0.001	
	smoking	0.286	-1.024	0.306	(NS)
	age	0.996	4.917	0.0001	

Alcohol consumption irregularly contributed to liver enzyme modifications (Table 2), with a positive coefficient when AST or GGT were considered, a negative coefficient when ALP was taken into consideration, and no statistical significance with ALT. On the contrary, in multiple regression analysis coffee consumption always demonstrated a significant and unequivocal trend toward reduction of all liver enzymes (Table 2).

No data are available in the literature on this topic, but it seems to be that liver enzymes are a target for coffee components. Modifications of enzyme synthesis or release could be invoked. However, although caffeine-induced haemodynamic changes can be supposed (3), they probably did not play a role in this effect. In fact, although in our survey ALP serum levels were significantly lower in subjects having lower blood pressure values (Fig. 3) and bilirubin was lower in those having lower cardiac contractility (Fig. 4), no relation was found between these haemodynamic parameters and coffee consumption.

Experimental and clinical studies involving the effects of coffee on liver enzymatic kinetics are in order.

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