Serum Magnesium, Cholesterol, and Lipoproteins in Patients with Atherosclerosis and Alcoholism

Some Preliminary Observations

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ALTHOUGH the incidence of atherosclerosis in chronic alcoholic subjects has been thought to be low,[1,2] this clinical dictum has not been adequately supported. Older studies often failed to distinguish between medial sclerosis and intimal atheromatosis[1] and failed to present experimental data.[2] Recent autopsy observations have been inconclusive and are retrospective in orientation.[3,4] Experimental studies on different animals under varying conditions have produced conflicting results. The ingestion of alcohol afforded some protection against the development of atherosclerosis in rabbits,[5] but was without apparent effect in fowls[6] and intensified the lesions in rats.[7] There is no convincing evidence at this time to indicate that any relationship between alcoholism and the severity of atherosclerosis exists in humans.

The results of measurements of serum cholesterol, lipoproteins, and magnesium in a group of acute and chronic alcoholic patients are presented in this study. The serum cholesterol and beta lipoprotein concentrations have been shown to be higher, on the average, in patients with coronary heart disease.[8,9] Perhaps, because of the large variations which occur between patients and in the same patient from time to time, the predictive value of these determinations is of a low order in a population such as the United States. However, in the presence of large and consistent differences in the serum cholesterol level between groups, such as Guatemalans[10] or Bantus[11] compared to people in the United States, differences in the rate of development of atherosclerosis have been demonstrated. The blood levels of magnesium and cholesterol may be inversely related. Bersohn and Oelofse[11] reported that the South African Bantu, among whom myocardial infarctions are rare, have significantly higher serum magnesium and lower cholesterol levels than European whites. The possible significance of magnesium in atherosclerosis has been indicated by animal experiments. In growing rats the severity of atherosclerosis produced by cholesterol and cholic acid feeding was greater in the presence of magnesium deficiency.[12] Furthermore, serum magnesium levels have been reported to be low in alcoholics with delirium tremens.[13] These blood constituents were utilized as indices of possible atherosclerosis because of the impos-

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sibility of diagnosing this disease in the absence of its overt manifestations.

MATERIAL AND METHODS

All patients were seen at least once during their hospitalization by one of us (O. M. J.). Patients were classified as acute alcoholics in the presence of signs of delirium tremens. Twenty-one of these patients were tremulous at their worst, 14 developed hallucinations, and one patient was comatose. The diagnosis of chronic alcoholism was based upon the standard history obtained from patients and/or relatives. Other diseases, usually precipitating hospitalization, were often present, including pneumonia in 13, convulsive disorders in 7, various traumatic conditions in 4, and acute pancreatitis in 2. Liver disease was known to be present in less than a third of these patients, but the entire "liver battery" was not obtained in all patients. In 8 of these alcoholics hepatic coma supervened. The diagnosis was based on the characteristic "flapping tremor."[14]

The diagnosis of atherosclerosis was based solely upon either myocardial alterations, confirmed by electrocardiograms, or upon a cerebral thrombosis in the absence of other possible causes for the neurologic signs. Most patients with cerebral thromboses were seen by the neurologic service in routine consultation and the diagnosis confirmed. It is clearly understood that significant atherosclerosis may be present in the absence of all overt signs by which a clinical diagnosis may be made.

The 12 "controls" were healthy-appearing laboratory personnel in the third and fourth decades. Their nutritional status was considered good, and their alcohol intakes were no greater than occasional "social drinks." This group was accepted despite the demonstration at autopsy of significant amounts of atherosclerosis in individuals of these age groups.[15]

The nonalcoholic patients with liver disease had obvious hepatic disorders with evidence of parenchymal involvement. All patients denied alcoholism and their liver involvement was considered generally as not caused by alcohol.

Serum magnesium was determined by EDTA titration according to the method of Hildebrand and Reilley,[16] cholesterol by the method of Carpenter,[17] and protein fractions and lipoproteins by paper electrophoresis.[18] The latter are reported as areas measured by densitometry. Total proteins were measured by the micro-Kjeldahl method.

RESULTS

Table I shows the average serum magnesium, cholesterol, lipoproteins and total protein levels in the control subjects, patients with atherosclerosis, the alcoholics, and the nonalcoholics with liver diseases. The average serum magnesium ranged from 1.69 mg per 100 ml in the patients with atherosclerosis to 1.91 in the controls. The lowest cholesterol levels (174 mg per 100 ml) were seen in the alcoholics and the highest (204 mg per 100 ml) in the controls and the patients with atherosclerosis. None of these differences reach statistical significance. The only statistically significant differences found for alpha lipoproteins ($p<0.05$) are those between the controls and the atherosclerotic patients. The beta lipoprotein values of the atherosclerotics are significantly different from each of the other

TABLE I

Average Serum Levels of Magnesium, Cholesterol, Lipoproteins, and Total Proteins and Its Fractions

	No. patients	Magnesium (mg/100 ml)	Cholesterol (mg/100 ml)	α-Lipoproteins (sq cm)	β Lipoproteins (sq cm)	Total proteins (g/100 ml)	Albumin	Globulin			
								α_1	α_2	β	γ
								(g/100 ml)			
Controls	12	1.91	204	2.2	8.5	7.21	4.50	0.29	0.47	0.81	1.14
Atherosclerotics	23	1.69	204	5.3	11.5	6.81	3.22	0.41	0.74	1.04	1.40
Alcoholics	66	1.85	174	3.9	8.2	6.57	2.89	0.47	0.70	1.08	1.43
Nonalcoholics with liver disease	9	1.76	179	2.6	9.6	6.50	2.68	0.41	0.53	0.80	2.08

TABLE II

Magnesium, Cholesterol, and Lipoprotein Findings in Alcoholic Patients with Atherosclerosis

Patient No.	Age	Sex	Alcoholic intake	Atherosclerotic manifestation	Serum magnesium (mg/100 ml)	Cholesterol (mg/100 ml)	α Lipoproteins (sq cm)	β Lipoproteins (sq cm)
1	67	M	1 pt per day	Remote myocardial infarction	1.98	123	7.0	12.5
3	74	M	"Heavy" until 4 years ago; now "less"	Coronary insufficiency	2.40	192	5.0	14.3
24	71	M	"Heavy"	ASHD* with congestive failure	0.86	134	3.8	8.0
42	85	M	"Moderately heavy	Cerebral thrombosis and ASHD	1.25	194	10.5	9.1
69	63	M	"Moderately heavy"	Cerebral thrombosis	2.16	86	3.7	5.3
173	71	M	"Heavy"	Cerebral thrombosis	0.78	182	5.6	13.4
				AVERAGES	1.57	152	5.9	10.4

* ASHD = Arteriosclerotic heart disease.

TABLE III

Clinical and Laboratory Data Obtained from Alcoholic Patients with Liver Coma

Patient No.	Age	Sex	Date	Serum magnesium (mg/100 ml)	Cholesterol (mg/100 ml)	α Lipoproteins (sq cm)	β Lipoproteins (sq cm)	Clinical status
4	48	M	1/15	1.80	59	1.8	4.7	Tremulous
			1/24	3.27	52	1.8	4.9	Liver flap; lethargic; died in 3 days
6	44	F	1/14	1.74	162	3.5	8.1	Conscious and clear
			2/10	2.32	202	3.1	5.4	Clear; liver flap had been present the day before
			2/21	2.67	126	3.1	7.1	Liver flap; died in 9 days
13	48	M	1/21	2.11	146	5.1	8.9	Stuporous, with signs of severe liver impairment; died next day
105	39	M	3/27	<0.30	345	0.8	12.1	Clear mentally
			3/31	2.40	290	1.0	10.2	Delirium tremens with hallucinations
			4/2	2.64	354	1.1	5.6	Mentally dulled, with liver flap
			4/10	2.60	280	2.6	23.1	Liver coma has cleared
109	38	M	3/31	2.70	152	3.9	8.7	Stuporous
			4/2	1.50	144	4.0	5.5	Confused
			4/8	1.20	138	2.0	7.4	Clearing
129	44	F	4/15	1.04	100	3.2	9.6	Mentally dulled; liver flap not elicited
			4/16	1.30	88	3.6	10.3	Stuporous
			4/18	2.97	104	0.9	5.4	Comatose; oliguria; died next day
138	43	M	4/21	2.37	114	1.5	8.8	Mentally clear
			4/24	3.57	125	2.6	11.5	Disoriented; liver flap
141	34	M	4/22	2.08	283	1.9	3.3	Mentally clear
			4/25	1.91	204	2.0	10.1	Confused and hallucinating with tremor but no flap
			5/5	3.81	132	2.2	9.5	Jaundice increasing; liver flap
NON-COMA AVERAGE				1.41	191	2.2	8.2	
COMA AVERAGE				2.97	149	2.6	7.7	

groups ($p<0.05$). The total serum proteins and their fractions are also tabulated. These are generally comparable except for the gamma globulins, which are elevated in all groups when compared to the controls.

The findings in the six patients in whom alcoholism and atherosclerosis coexisted are summarized in Table II. These patients had been included in Table I with the patients with atherosclerosis, not with the alcoholics. All

TABLE IV

The Effect of Delirium Tremens on Serum Magnesium, Cholesterol, and Lipoproteins

Patient No.	Age	Sex	Date	Clinical status	Magnesium (mg/100 ml)	Cholesterol (mg/100 ml)	α Lipoproteins (sq cm)	β Lipoproteins (sq cm)	Other diseases
2	45	M	1/13	Hallucinating	2.88	142	4.6	8.4	—
			1/20	Clear	2.70	138	2.3	4.4	—
8	35	M	1/16	Tremulous	2.64	198	5.7	6.1	—
			1/17	Clear	1.86	226	5.3	8.9	—
11	48	F	1/20	Tremulous	0.78	230	5.6	4.5	—
			1/23	Comatose	1.77	202	7.6	8.6	—
			1/24	Comatose	1.50	192	7.5	12.2	—
			2/3	Hallucinating	1.70	183	5.1	10.8	—
			2/14	Clear	2.37	216	4.0	12.9	—
12	49	F	1/21	Hallucinating	2.16	138	5.5	6.7	—
			1/23	Clear	1.65	164	1.8	5.4	—
17	48	M	1/27	Tremulous	2.55	178	4.5	8.0	—
			1/29	Tremulous	1.83	146	5.5	11.7	—
			2/3	Tremulous	1.81	152	3.1	7.1	Duodenal ulcer
19	30	M	1/27	Hallucinating	3.30	210	2.5	7.6	Fracture; pneumonia
			1/31	Tremulous	0.96	102	2.9	5.9	Died
38	50	M	2/5	Hallucinating	1.18	224	3.4	3.7	—
			2/7	Clear	2.04	234	6.9	10.5	—
36	68	M	2/5	Tremulous	2.32	226	3.1	5.9	—
			2/6	Tremulous	2.18	218	4.8	6.6	—
40	57	M	2/7	Tremulous	1.44	243	6.4	7.1	—
			2/10	Tremulous	1.82	230	3.7	8.2	—
46	53	M	2/11	Hallucinating	2.16	224	5.7	10.2	—
			2/13	Clear	2.46	206	9.1	11.1	—
50	50	F	2/13	Tremulous	1.62	152	1.7	6.7	Pneumonia
			2/19	Tremulous	2.38	156	5.9	12.8	—
61	45	M	2/25	Tremulous	2.78	168	3.5	3.6	—
			2/27	Tremulous	2.01	160	5.4	8.7	—
			3/3	Clear	1.77	146	4.3	10.2	—
77	45	M	3/10	Tremulous	2.39	156	5.8	6.5	—
			3/11	Clear	2.05	160	5 5	8.5	—
88	48	F	3/17	Tremulous	0.97	228	8.8	7.3	—
			3/18	Clear	<0.3	248	10.4	11.1	—
			3/20	Hallucinating	0.58	234	14.0	15.1	—
			3/24	Clear	0.58	212	5.8	8.8	—
105	38	M	3/27	Clear	<0.3	345	.8	12.1	—
			3/31	Hallucinating	2.40	290	1.0	10.2	—
			4/2	Liver coma	2.64	354	1.1	5.6	—
			4/10	Clear	2.60	280	2.6	23.1	—
108	59	M	3/28	Tremulous	1.80	162	3.8	9.9	—
			3/31	Clear	2.10	173	4.0	7.2	—
120	49	M	4/10	Tremulous	1.16	172	4.6	5.6	—
			4/11	Clear	1.70	197	6.2	9.0	—
121	53	M	4/10	Hallucinating	1.74	148	1.9	6.4	—
			4/11	Confused	1.43	150	6.5	12.9	Pneumonia
			4/14	Tremulous	1.37	122	2.0	8.0	—
132	38	M	4/15	Tremulous	1.83	268	7.2	16.9	—
			4/16	Clear	1.78	260	5.8	18.9	—
141	34	M	4/22	Clear	2.08	288	1.9	3.3	—
			4/25	Hallucinating	1.91	204	2.0	10.1	—
			5/5	Clear; liver flap	3.81	132	2.2	9.5	—
143	50	F	4/23	Tremulous	qns	146	8.0	9.3	—
			4/24	Hallucinating	1.19	255	6.3	6.1	—

TABLE IV (*Continued*)

Patient No.	Age	Sex	Date	Clinical status	Magnesium (mg/100 ml)	Cholesterol (mg/100 ml)	α Lipoproteins (sq cm)	β Lipoproteins (sq cm)	Other diseases
143, *cont.*			4/25	Clear	1.09	157	6.2	6.3	? Drinking ward alcohol
			4/28	Clear	2.18	186	3.7	6.5	—
155	43	M	5/8	Tremulous	1.91	182	3.9	7.7	—
			5/9	Hallucinating	1.63	178	4.4	10.2	—
			5/12	Clear	1.63	182	3.9	11.9	—
156	55	M	5/8	Clear	2.72	156	3.0	7.8	Subtotal gastrectomy, remote
			5/9	Hallucinating	1.63	162	2.9	8.8	—
			5/12	Hallucinating	3.00	184	1.2	7.9	—
			5/20	Clear	1.31	206	2.0	11.9	? Marginal ulcer
163	45	M	5/19	Hallucinating	1.36	154	5.7	5.8	—
			5/20	Tremulous	1.05	160	3.7	5.6	—
				Admission Average	1.90	197	4.5	7.4	—
				Final Average	1.92	186	4.2	9.7	—

admitted to heavy alcoholic intakes, but one patient claimed he had lessened his intake during the preceding four years. Data on dietary histories are scanty. Several patients admitted inadequate food intake but only one patient was considered by clinical examination to be "not well nourished." In this group the serum magnesium levels averaged 1.59 mg per 100 ml and the cholesterol 152 mg per 100 ml, both lower than the corresponding values in the alcoholics and the atherosclerosis group as a whole. The alpha lipoprotein was 5.9 sq cm, and the beta 10.4 sq cm, approximately equal to that of the entire atherosclerosis group and higher than that in the alcoholics.

In Table III are the results obtained in eight alcoholic patients in whom severe liver disease was present, leading to the development of hepatic coma. In one patient, OJ-109, coma was present initially and there was subsequent gradual improvement. The noncoma average for magnesium was 1.41 mg, cholesterol 191 mg, both per 100 ml, alpha lipoproteins 2.2 sq cm; and beta lipoproteins 8.2 sq cm. In comparison to the values observed in the alcoholics, the magnesium and alpha lipoproteins are lower, and the cholesterol and beta lipoproteins are higher in the precoma patients. With the development of hepatic coma there was a marked increase in the serum magnesium (or, conversely, a pronounced decrease in serum magnesium in the patient with clearing of the coma). The cholesterol levels fluctuated in the individual patients but evidenced a tendency to decrease and fell to an average of 149 mg per 100 ml during coma. The alpha lipoproteins were essentially unchanged. The beta lipoproteins varied with gross irregularity, and the average during coma was 7.7 sq cm, which was somewhat less than the average for all alcoholics.

In Table IV the results in 24 alcoholics with delirium tremens are compared at admission and following varying periods of hospitalization. The initial levels of serum magnesium, cholesterol, and lipoproteins generally corresponded to the time of the most intense signs of alcoholic delirium. Of these patients, 1 was comatose, 13 had hallucinations, and 10 were tremulous. At the time of the final determination all patients were improving and most were clear mentally. The final averages are similar to the initial levels, except for some increase in the beta lipoproteins from 7.4 to 9.7 sq cm. These similarities occurred in the face of extensive individual variability. With clinical improvement in the intensity of the delirium the serum magnesium fell in 11 patients, increased in 8. In 6 patients with clinical deterioration during hospitalization, the magnesium increased in 3 and declined in 3. Both the beta lipoprotein and serum cholesterol also

varied—the lipoproteins increased in 17 and fell in 7 and the cholesterol increased in 10 and fell in 13 patients. However, there was no consistent pattern in these alterations and no correlation was apparent among the changes or between them and such clinical phenomena as improvement or worsening, return of appetite and increased food intake, or the preceding nutritional history or status of the patients.

DISCUSSION

Although these preliminary results do not answer the old question regarding the frequency of atherosclerosis in alcoholics, the data contain no suggestion that the alcoholic is spared the rigors of atherosclerosis. There is no significant difference between the cholesterol and beta lipoprotein levels in the few controls reported and the alcoholics, nor do the serum cholesterol values appear grossly different from "normal" values appearing in the literature.[8,9] This is consistent with an equal predisposition toward atherosclerosis. Clinical evidence of atherosclerosis did occur in 6 of our alcoholics. None of these exhibited abnormally high serum cholesterol values.

These 6 alcoholics with atherosclerosis are considerably older than the average of the entire group of alcoholics. A time factor has been operative and their survival beyond 63 years allowed them to arrive in the decades in which atherosclerosis becomes frequent. The absence of advanced complications of alcoholism in these patients is significant, at least in permitting this survival to occur. However, the data do not indicate that one such complication, liver disease, has any effect on the occurrence of atheromatous disease, other than the possible shortening of life. The serum beta lipoproteins and cholesterol levels in the alcoholics with liver coma are essentially the same as those in the alcoholic group as a whole. Similarly, in the nonalcoholics with liver disease the cholesterol and beta lipoprotein values are not grossly different from the controls or alcoholics.

The relationship between serum cholesterol or beta lipoproteins to coronary atherosclerosis has been studied more extensively than have these two variables and cerebral atherosclerosis. Epidemiologic studies have indicated that in certain areas of the world, particularly in Japan,[19] there exists a marked difference in frequency between coronary and cerebral atherosclerosis, the latter being more prevalent. The validity of causes of death obtained from death certificates is open to question.

Morphologically, however, the atherosclerotic lesions of both the coronary and cerebral arteries are similar. For this reason our patients with cerebral thrombosis were considered part of this atherosclerotic group. In any event, the exclusion of this small group of patients would not alter the results of this study.

The variations in serum cholesterol and magnesium levels in the same patient were often larger than might be expected. When a serum magnesium level appeared unusually low, the serum was reanalyzed for magnesium. However, none of the methods usually used for the magnesium determinations have been extremely reliable in our laboratory. Repeated determinations upon a series of serums resulted in a standard deviation of 0.2 mg per 100 ml. If the outside limits are considered to include three standard deviations then a serum containing 1.0 mg per 100 ml might occasionally yield a value as low as 0.4 mg per 100 ml. Hence, individual determinations cannot be considered too seriously. On the other hand, it is clear that the method is adequate to demonstrate average differences in groups of patients. This is demonstrated in the present data by the rise in serum magnesium in patients developing hepatic coma. The concomitant changes in serum cholesterol and lipoproteins were not consistent.

In our patients with delirium tremens serum magnesium was frequently within normal limits and, despite considerable individual variability, there was no significant change in the group average with hospitalization and clinical improvement. We have been unable to relate serum magnesium to the development of delirium tremens.

The elevation of gamma globulins in the atherosclerotic patients was unexpected. It cannot be explained solely on the basis of liver disease, since it occurred also in its absence.

CONCLUSIONS

The results of this study do not support the concept that overt atherosclerosis is less frequent in the chronic alcoholic. No significant differences in serum cholesterol and lipoprotein fractions were found.

We have not been able to demonstrate a correlation between serum magnesium and serum cholesterol levels. Beta lipoproteins were elevated in the atherosclerotic group.

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