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ALCOHOL AND NUTRITION: Caloric Value, Bioenergetics, and Relationship to Liver Damage

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CONTENTS

INTRODUCTION

Alcoholic beverages contribute significantly to overall calories in the diet of most Western countries. Numerous effects of ethanol on intermediary metabolism and on nutrition have been described. This chapter reviews the dietary contribution of calories derived from alcoholic beverages and their metabolic utilization as a source of energy. The interaction between alcohol and nutrition in the development of alcoholic liver damage is discussed as an example of how ethanol and nutrition may contribute to the pathogenesis of disease in man.

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In recent years, investigators have examined the composition of the diet in the United States and other Western countries. These investigations have been engendered by well-documented relationships between intake of various dietary components and the incidence of disease. In particular, there is interest in the extent to which ethyl alcohol contributes to the total caloric intake.

DIETARY SURVEYS OF ALCOHOL CONSUMPTION

Total per capita alcohol consumption in the US increased slowly, but steadily, from 1934 to 1980 (67). Since 1980 alcohol consumption has leveled off and perhaps decreased slightly. Similar trends have been reported for other Western countries (86, 93). In 1955, alcoholic beverages accounted for 3.0% of total per capita caloric intake, rising to 5.7% in 1955, while in the US alcohol contributed 4.5% to the total intake of calories (81). These figures represent aggregate approximations derived from tax and census records and information regarding the national food supply. Children and abstainers were not excluded. Although census studies do not provide information about the distribution of alcohol consumption within the population, their advantage is that the data obtained are not influenced by subject recall and the results of alcohol beverage sales are known accurately.

Dietary surveys including assessment of alcohol consumption have been carried out in both alcoholic and nonalcoholic individuals. In one survey over 80% of male business executives and professionals drank alcohol on one or more of the study days. Within this group of drinkers, ethanol accounted for 5–10% of total calories in one fourth of the subjects, while in an additional one fourth ethanol averaged more than 10% of calories (5).

Similar results have been obtained in other nationwide surveys. A wide geographic variation was reported in prevalence of alcohol consumption in both men and women enrolled in nine Lipid Research Clinics between 1972 and 1975. The highest consumption was in southern California whereas the lowest was in Oklahoma. These surveys did not include weekend alcohol consumption. In drinkers, alcohol accounted for 6.5–15.2% of calories ingested by men and 6.0–18% by women in the 24 hours before the survey (27). In the National Food Consumption Survey, a national probability sample (99), alcoholic beverages contributed 17.0% for male drinkers and 21.9% for female drinkers. However, ethanol per se, accounted for only 5.3% of calories in the group after calories from carbohydrate and protein in beer were subtracted.

Although data from surveys are subject to the imperfections of recall and imprecise quantitation, the results obtained are similar to those obtained by weighing all food consumed by the crew of an oil tanker during an 8-day sea voyage. Total caloric intake in these British sailors was 3600 kcal/day, of which

13% was from ethanol. Again, there was a wide range, from 5 to 20% of total calories (29).

Despite this appreciable contribution of alcohol to total calories, protein intake is seldom changed, either as an absolute amount or as a percentage of total calories. However, consumption of fat and carbohydrates is more variable in drinkers (Table 1). In British sailors, alcohol calories tended to be substituted for fat. Fat accounted for 38% of the calories in light drinkers (5% calories as ethanol) vs 24% in moderate drinkers (20% ethanol). Furthermore, consumption of simple carbohydrates in the form of sugars and sweetened soft drinks was decreased in moderate drinkers (15, 29). Although there is often an inverse relationship between calories derived from ethanol and from fat or carbohydrate, some surveys have found that alcohol calories are added to the diet rather than replacing other foodstuffs. In the group surveyed by Bebb and colleagues, alcohol calories were added to the diet on drinking days compared with nondrinking days (5). In the Zutphen study of obesity and dietary intake, there was a significant positive correlation between the degree of fatness and alcohol intake, whereas the correlation between obesity and total caloric intake was negative (45). Obese men consumed almost twice as much alcohol as lean men. Although total calories ingested and alcohol consumption were not compared directly, the relationship would be inverse almost by necessity. More information regarding the relationships between caloric balance, dietary alcohol intake, and body weight in nonalcoholics would be important, particularly to assess utilization of alcohol as an energy source in moderate drinkers.

Table 1 Dietary surveys including alcohol consumption in nonalcoholics

				% Total Calories			
Study	Method	Subjects (number)	Total kcal	EtoH	Prot	Fat	CHO
Bebb et al (5)	3-day diary	men (114)	2348	6.1	16.0	38.1	39.8
	× 6 sets	drinkers (94)	2391	6.2	15.0	38.0	38.8
		nondrinkers (20)	2145	0	16.5	38.8	44.7
Dennis et al (27)	24-hr recall	men (1993)	2400–3200	6–15[a]	~15[b]	36–43	43-46
	Lipid Res. Clin.	women (1741)	1650-2150	6–18[a]	~15[b]	36–43	40–45
Eddy et al (29)	food	British seamen	3600	13.0	12.0	35.0	40.0
Kromhout (45)	cross-check	men (871)					
	usual intake	obese	2916	1.6	11.5	42.1	43.4
	6–12 months	nonobese	3193	0.6	11.8	43.1	45.5
Windham et al (99)	24-hr recall	Age > 14 yr (7061)					
	& 2-day dairy	drinkers	2037	5.30	16.3	40.3	38.1
		nondrinkers	1928	0	17.2	41.4	41.4

[a]Drinkers only.
[b]Men and women combined.

Not surprisingly, alcohol contributes an even greater percentage to the total caloric intake of alcoholics. Assessment of dietary intake and nutritional status of alcoholics is often confounded by socioeconomic variables and availability of nutrient intake. These factors must be controlled in order to assess accurately nutrition-alcohol interactions. Hurt and coworkers (37) at the Mayo Clinic found from dietary reports that total calories ingested by 12 employed alcoholics were almost identical to total calories consumed in the hospital during and after alcohol detoxification. These alcoholics replaced alcohol calories with carbohydrates while undergoing detoxification. Of interest, 88% of 59 alcoholics in this same study were at or above ideal body weight. Nutrient intakes in these individuals were equal to or greater than RDA for total protein, calories, and most other nutrients, despite an average consumption of 35% of calories as ethanol (approximately 150 g). Neville and coworkers (68) reported a similar caloric contribution of alcohol to the diets of lower middle class alcoholics. Percentages of protein, fat, and carbohydrate calories were decreased equally in alcoholics compared to controls. However, vitamin B intakes were similar to controls. Although urinary vitamin excretion increased slightly after abstinence in the hospital, there was no evidence of gross deficiencies.

Careful assessment of nutritional parameters including anthropometrics, serum proteins, and immunologic competence in alcoholics has shown evidence of malnutrition in most, but not all, patients (17, 58, 65, 84). In one study, tricep skin-fold thickness and mid-arm and muscle circumference were inversely correlated with alcohol consumption (84). Alcohol intake in these patients averaged 25–35% of total calories. It must be emphasized that these findings were obtained from alcoholics who were otherwise healthy and had no clinical or laboratory evidence of liver disease. As discussed later in this chapter, the incidence of malnutrition is much greater in patients with alcoholic liver diseases, particularly alcoholic hepatitis and cirrhosis.

CALORIC VALUE OF ETHANOL

Ethanol yields 7.1 kcal/g upon complete combustion in a bomb calorimeter. To assess the effectiveness of alcohol as an energy source, two experimental approaches have been used. Metabolic studies directly measure thermogenesis and oxygen consumption to assess energy metabolism from ingested ethanol. The second approach correlates alcohol intake with body weight or anthropometric measurements. Both approaches have produced conflicting data. The classical report of Atwater & Benedict (3) demonstrated in three healthy nonalcoholic volunteers that 72 g of absolute ethanol per day was utilized as efficiently as fat or carbohydrate as a source of energy. In this study, energy utilization was measured by direct calorimetry. Only during vigorous exercise was there a suggestion that ethanol calories were not efficiently utilized and the difference was considered by the authors to be within experimental error. In support of the findings of Atwater & Benedict, Barnes and coworkers (4) did not observe an increase in oxygen consumption or thermogenic effects of 31.5 g ethanol per 65 kg body weight in nine normal subjects. In contrast, Perman (70) reported that administration of moderate doses of alcohol to normal subjects resulted in thermogenesis and increased oxygen consumption, which suggests inefficient caloric utilization of ethanol.

In some studies of alcohol feeding, subjects have lost weight while receiving alcoholic beverages (13, 57, 71, 72). In one study, weight loss occurred in volunteers when 35% of carbohydrate calories were replaced by ethanol and was maximal at 50%, the highest range tested (71). Furthermore, addition of ethanol to the diet resulted in a transient small increase in weight that returned to baseline in 10 days, whereas increases in dietary fat and carbohydrate calories resulted in greater weight gain that was sustained over a similar time. In addition, ethanol (unlike fat or carbohydrates) failed to stabilize weight in obese subjects on hypocaloric diets (13).

These important observations suggest that the caloric utilization of ethanol may be dose-related. At intakes less than 25–35% of calories, ethanol may be completely utilized as a source of energy, but at higher intake utilization may not be complete. At high doses ethanol may be metabolized by pathways other than those that metabolize low doses (32, 36, 49, 50, 60, 63, 64, 79, 83, 97). Furthermore, high concentrations of ethanol and its metabolites may affect ATP formation and turnover, as discussed later in this chapter. It is possible that effects of ethanol on caloric utilization might be mediated indirectly through inefficient utilization of other dietary components. For example, urinary nitrogen losses were higher in subjects receiving 25% of calories as wine compared with control periods (57).

Not all studies have shown a negative effect of alcohol on body weight. In several surveys alcoholics were at or above ideal body weight (17, 28, 45, 47, 58, 65, 84). In the Zutphen study a positive correlation was found between alcohol consumption and obesity. This observation is consistent with effective caloric utilization of ethanol in real-life situations, particularly in light of the lower total calories ingested by obese men in this study (45).

BIOENERGETICS OF ETHANOL METABOLISM

General Considerations

Alcohol dehydrogenase (ADH), a cytosolic enzyme that exists as several isoenzymes, is the major enzyme metabolizing ethanol (49, 61). ADH catalyzes the oxidation of ethanol to acetaldehyde while converting the cofactor NAD^+ to NADH. Acetaldehyde is further metabolized to acetate by aldehyde dehydrogenase (ALDH), which has both mitochondrial and cytosolic forms (49). NADH is generated from the cofactor NAD^+. These reactions are summarized as

$$\text{ethanol} + NAD^+ \rightleftarrows \text{acetaldehyde} + NADH \tag{1.}$$

$$\text{acetaldehyde} + NAD^+ \rightleftarrows \text{acetate} + NADH. \tag{2.}$$

Metabolism of ethanol by ADH and acetaldehyde by ALDH generates reducing equivalents (NADH) that can be used for mitochondrial ATP synthesis. The low K_m for ADH (1 mM) makes it the principal enzyme for ethanol metabolism in vivo (49, 61).

Other enzymes are capable of metabolizing ethanol. Of these only the microsomal ethanol oxidizing system (MEOS) is believed to be active in vivo (32, 44, 49, 64, 83, 97). As implied by the name, this enzyme is bound to the smooth endoplasmic reticulum of hepatocytes and resembles the cytochrome P-450 mixed-function oxygenases in its catalytic activity. MEOS differs from ADH in several aspects. It has a higher K_m, on the order of 10 mM compared with 1 mM for ADH (49, 61). The higher K_m of MEOS suggests that the enzyme would be active in vivo only at high ethanol concentrations. Secondly, its activity increases after chronic ethanol feeding due to induction of the enzyme in animals (40, 50, 63, 64) and in man (44, 64, 79). Thus, MEOS may be quantitatively more important in regular heavy drinkers. Recent evidence suggests that MEOS metabolizes ethanol in vivo in deermice, which lack ADH, and at high ethanol concentrations (83). Finally, NADPH rather than NAD^+ serves as a cofactor and $NADP^+$ is formed rather than reducing equivalents for potential ATP synthesis. Acetaldehyde is the product of MEOS-catalyzed oxidation of ethanol, just as in ADH-catalyzed ethanol oxidation:

$$\text{ethanol} + NADPH + H^+ + \tfrac{1}{2}\,O_2 \rightarrow \text{acetaldehyde} + NADP^+ + H_2O.$$

The acetaldehyde formed is further metabolized by ALDH.

Pirola & Lieber (71, 72) proposed that metabolism of ethanol by MEOS results in loss of energy (thermogenesis) without effective coupling to ATP synthesis. This hypothesis might explain the weight loss observed in subjects receiving 50% of dietary calories as ethanol (71). If correct, oxygen consumption should be higher during ethanol oxidation in animals chronically fed ethanol and in human alcoholics. Increased oxygen consumption has been observed after ethanol administration in man in some studies (41, 70, 92) but not in others (3, 4). Conflicting results have also been obtained in experimental animals and are discussed later in this chapter.

If ethanol oxidation is to provide useful energy for other cellular processes, it must be coupled in some way to ATP production. During ADH-catalyzed oxidation of ethanol, one mole of NADH is formed for each mole of ethanol oxidized. Since this NADH is formed in cytoplasm, it must be shuttled into the mitochondria for use in ATP synthesis. The major shuttle system for this transport is the malate-aspartate system (11, 19, 25, 26, 49, 76). In this context, several studies suggested that the shuttle might be limiting for ethanol metabolism (11, 76). However, more recent data provide evidence that the mitochondrial shuttle is capable of operating at rates in excess of those of ethanol metabolism (26). However, during fasting shuttle intermediates may become depleted, which would make mitochondrial transport and reoxidation of NADH rate limiting (19, 25). Thus, it seems unlikely that the shuttle system limits ethanol metabolism or mitochondrial access to NADH except possibly during fasting.

Effects on Hepatic ATP Content

Through the processes of electron transport and oxidative phosphorylation, free energy gained during oxidation of both ethanol and acetaldehyde is used for synthesis of ATP, which may later be used to drive cellular processes such as biosynthesis and maintenance of electrochemical gradients. Within 15 min after administration of a single intraperitoneal dose of ethanol (approximately 0.5 g/kg) both the cytoplasmic and mitochondrial NAD^+/NADH ratios were decreased (94). There was a corresponding increase in the phosphorylation potential that was attributed, in part, to metabolism of ethanol beyond acetaldehyde. It is of note that the absolute levels of ATP did not decrease and were occasionally increased after single-dose ethanol administration to intact rats (33, 36, 94) or after perfusion of the isolated rat liver with 10-mM ethanol (98). Thus, acute administration of ethanol does not decrease hepatic ATP content, but may increase it slightly.

However, there is evidence to suggest that hepatic ATP content is reduced after chronic ethanol feeding (1, 8, 14, 33, 35, 85, 96). This decrease in hepatic ATP content could be due to either increased utilization of ATP in response to increases in hepatic "ATP-ase" activity or to decreased synthesis of ATP.

Effects on Hepatic "ATP-ase" Activity

Increased activity of hepatic Na-K ATP-ase would be expected to increase ATP utilization by the liver, in effect creating a hypermetabolic state. This hypothesis was proposed by Israel and coworkers, who consistently observed increases in oxygen consumption in liver slices (95) and in perfused livers (9, 39, 91) from rats chronically fed ethanol. In these same animals, there was a corresponding increase in activity of the sodium pump (70%) and Na-K ATPase

(190%). Furthermore, the reported increase in O_2 consumption was completely eliminated by ouabain, an inhibitor of Na-K ATPase (9, 10).

On the basis of these observations, the investigators suggested that the increased metabolic demands might increase susceptibility of the alcoholic liver to damage from hypoxia (39). In other studies, oxygen consumption was unchanged in perfused livers (80) or in isolated hepatocytes (18) from fasted chronic ethanol-fed rats. Although hepatic vein O_2 tension was lower in fasted ethanol-fed baboons, it actually increased after ethanol administration (82). It has been suggested that changes in availability of substrates in fasted, ethanol-fed animals may account for the observed increases in O_2 consumption (2, 19, 22, 35). Other reports indicate that the magnitude of increase in Na-K ATPase is only 15% (35), an amount unlikely to account for changes in ATP levels.

Effects on Oxidative Phosphorylation

Decreased synthesis of ATP has been reported in animals fed ethanol for more than one month (1, 14, 35, 85, 96). Gordon reported that ATP synthesis was decreased in rats with ethanol-induced fatty liver. This decrease resulted from accumulation of long-chain CoA derivatives of fatty acids, which impede translocation of ADP into mitochondria and thereby limit the rate of oxidative phosphorylation (35). Using isolated submitochondrial particles from the livers of rats fed ethanol for one month, Thayer & Rubin (89) observed a 35–40% decrease in ATP synthesis with each substrate tested (Table 2). These results suggested that the observed decreases in respiration were a consequence of alterations in the electron transport chain itself. Major decreases (40–50%) occur in activities of cytochrome oxidase, cytochrome b, and NADH dehydrogenase (7, 88–90).

Other studies have found decreases in respiration in intact mitochondria after chronic ethanol feeding (10, 14, 21, 85). In these studies, state-3 (ADP-stimulated) oxygen consumption was decreased in intact mitochondria from ethanol-fed rats, whereas state-4 (basal) oxygen consumption was unchanged (7, 21, 85). The decreases in ATP synthesis appear to be related to decreased catalytic activity of the ATP synthetase complex as measured by the ATP-P_i exchange rate (14, 21), rather than to alterations in the proton gradient (14).

Similar changes have been observed in hepatic mitochondria obtained from baboons fed ethanol for up to 7 years. In these animals, there was a 50% decrease in state-3 respiration as well as a 25–40% decrease in enzyme activities of mitochondrial respiratory chain. Mitochondria from ethanol-fed baboons were larger than those from control animals and also exhibited morphologic evidence of damage, with disorganization of cristae even at the stage of fatty liver (2). Morphologic changes of this type have been frequently observed in experimental animals fed ethanol (34, 38, 43, 52) and in alcoholics (16, 42, 46, 54).

Table 2 Effects of chronic ethanol ingestion on oxidative phophorylation by rat hepatic submitochondrial particles[a]

Substrate	Parameter	Control	Ethanol[b]	Change (%)
NADH	Respiration rate[c]	151	99	−34
	P/O ratio	2.59	2.33	−10
	Phosphorylation rate[d]	389	230	−41
Succinate	Respiration rate[c]	145	104	−28
	P/O ratio	1.55	1.37	−12
	Phosphorylation rate[d]	225	146	−35
Ascorbate/phenzine methosulfate	Respiration rate[c]	131	98	−25
	P/O ratio	.92	.79	−14
	Phosphorylation rate[d]	120	79	−34

[a]Data are adapted from Thayer & Rubin (89).
[b]All results are significantly different from control ($p < 0.05$).
[c]Nanoatoms of oxygen/min/mg of protein.
[d]Nanomoles of ATP/min/mg of protein.

Effects of Acetaldehyde on Bioenergetics

Several studies have assessed the effects of acetaldehyde on mitochondrial function to determine what role, if any, this potentially toxic metabolite of ethanol has in causing the decreased ATP synthesis observed in chronic ethanol-fed animals. High concentrations (3–30 mM) of acetaldhyde inhibit oxidative phosphorylation and ATP-P_i exchange in freshly isolated hepatic mitochondria from untreated rats (20, 22). There was also decreased Ca^{2+} uptake in the presence of acetaldehyde concentrations in excess of 12 mM. In addition, there was decreased CO_2 production from citric acid cycle intermediates in the presence of acetaldehyde (1.25–3.0 mM) (22). In vivo, inhibition of aldehyde dehydrogenase by calcium cyanamide caused a decrease in phosphorylation potential (ATP/ADP · P_i) during infusion of ethanol or acetaldehyde. The decrease was due almost entirely to increases in ADP and P_i without significant decreases in ATP content (55). Although the results of these studies suggest that acetaldehyde may cause changes in mitochondrial energy production, the concentrations of acetaldehyde required to demonstrate these effects are far in excess of those occurring in the liver, even after ingestion of large amounts of ethanol.

It is of interest that the toxic effects of acetaldehyde on mitochondrial function can be prevented by addition of cysteine in vitro (23). The investigators attributed the protection in part to condensation of acetaldehyde with cysteine to form a stable adduct. Whether cysteine or other thiols such as glutathione are important in in vivo protection against acetaldehyde or ethanol-induced mitochondrial damage remains unknown.

Recent evidence suggests that acetate may alter energy utilization by increasing adenine nucleotide turnover (31, 74). Hyperuricemia and gout have long been associated with heavy ethanol consumption. In part, the increases in uric acid have been attributed to increased blood lactate levels (6, 56, 100). However, ethanol-induced elevation of urate production occurs as a result of increased turnover of ATP as well (74). The investigators hypothesized that increased turnover results from utilization of two moles of ATP for each mole of acetate converted to acetyl CoA:

$$\text{acetate} + \text{ATP} \rightarrow \text{PP}_i + \text{acetyl-AMP}$$

$$\text{acetyl-AMP} + \text{CoASH} \rightarrow \text{acetyl-CoA} + \text{AMP}.$$

The rate of acetate formation from ethanol exceeds the rate of hepatic acetate oxidation and thereby increases acetate loads to other tissues (74). Peripheral oxidation of acetate possibly contributes to the net increase in nucleotide turnover observed. Formation of acetate from ethanol could result in a net loss of ATP under these conditions.

ROLE OF ALCOHOL AND MALNUTRITION IN PATHOGENESIS OF ALCOHOLIC CIRRHOSIS

A close relationship between prolonged alcohol consumption and liver disease has been recognized for many years. In the United States, alcohol abuse accounts for 75% of cases of cirrhosis. The spectrum of liver injury produced by alcohol includes fat accumulation, alcoholic hepatitis, and cirrhosis. These three morphologic conditions are not mutually exclusive and may coexist within the same liver.

The pathogenesis of alcohol-related liver disease is complex. Both the amount and duration of alcohol consumption are important factors (47). Although there is a clear relationship between alcohol consumption and alcoholic hepatitis or cirrhosis, total alcohol consumption alone does not explain why only 17–30% of heavy drinkers develop alcoholic liver injury (47, 49). For this reason, other factors including genetics, immune response, and nutrition have been studied to determine which ones might contribute to pathogenesis of alcohol-related liver injury.

The relationship between nutrition and alcoholic liver disease has received much attention, but the role of nutritional factors in pathogenesis of alcoholic liver disease remains controversial (48, 60). Before 1960 liver disease in patients consuming large quantities of alcohol was thought to be due solely to protein malnutrition. That alcoholic liver disease might be due to nutritional deficiencies was supported by experiments showing that alcohol administered in the drinking water of rats did not produce liver damage unless accompanied by a nutritionally deficient diet (12). Epidemiologic studies reporting a reduced intake of protein and other essential nutrients in alcoholics with liver disease also supported the nutritional hypothesis (69). Furthermore, in uncontrolled studies the clinical signs of liver disease improved in patients given high-protein, vitamin-supplemented diets despite continued consumption of more than 100 g of ethanol per day (30, 87), while the clinical signs of liver disease worsened in patients who continued to drink alcohol and ate low-protein diets.

In 1963 Lieber and coworkers (53) demonstrated that rats fed 36% of calories as ethanol with an otherwise nutritious diet developed fatty liver. In these experiments, the natural aversion of rodents to alcohol was overcome by administering ethanol in a totally liquid diet. These observations were extended to primates such as the baboon (51, 78). These animals were fed 4.5–8.3 g of ethanol/kg of body weight, while pair-fed controls were given diets with carbohydrates isocalorically substituted for 9 months to 4 years. This amount of alcohol represented 50% of the total calories consumed, the average consumption of alcohol by alcoholic patients (Table 3). The entire spectrum of alcoholic liver injury was initially reported to occur in these animals, including fatty liver, alcoholic hepatitis, and cirrhosis (51, 78). It was subsequently noted that the histologic appearance of the livers from these animals was similar to but not identical with the histologic lesion of alcoholic hepatitis in humans (73). In the baboons, hepatocytes were increased in size and there was some ballooning of cells associated with mononuclear inflammatory cells. There were, however, few polymorphonuclear cells in the inflammatory infiltrate, a characteristic feature of alcoholic hepatitis. By electron microscopy there was some clumping in the cytoplasm of the liver cells but no frank alcoholic hyalin was seen. In other studies, administration of ethanol as 50% of the calories to monkeys for 4 years resulted only in fatty liver (62).

Administration of ethanol as 50% of total calories combined with a nutritious diet to alcoholic patients and nonalcoholic volunteers for two weeks, resulted in fatty liver and ultrastructural changes in mitochondria (54, 74). The later stages of alcoholic liver disease were rarely, if ever, seen in these patients (77). Thus, just as a solely nutritional explanation for alcoholic liver disease proved untenable, direct hepatotoxicity from alcohol alone inadequately explained the clinical, biochemical, and histologic observations in humans with alcohol-related liver injury.

Clearly the daily amount of alcohol consumed and duration of excessive consumption are important in the etiology of liver injury, but nutritional factors may play a role in modulating the hepatotoxicity of alcohol. The prevalence of malnutrition in alcoholics with liver disease is so high that it may be impossible to isolate completely the contribution of each factor. Recently the Veterans Administration Cooperative Alcoholic Hepatitis Study Group reported the incidence of protein/calorie malnutrition in a large number of patients with alcoholic hepatitis (58). This study excluded patients with nonspecific changes

Table 3 Dietary surveys in alcoholics with and without liver disease

Study	Method	Alcoholic subjects (number)	Total kcal	% Total calories EtoH	Prot	Fat	CHO
Hurt et al (37)	6-mo recall	not specified (58)	3118	34.9	11.0	30.3	22.8
Mendenhall et al (58)	1-mo recall	liver disease (21)	3722	41.5	8.1	18.5	30.8
		alcoholic hepatitis (95)[a]	3104	50.0	7.0	15.1	28.0
Mills et al (65)	6-mo recall	liver disease (30)	2452	52.0	9.5	N.A.	N.A.
Neville et al (68)		men[b] (26)	2710	36.4	10.0	22.6	31.0
		women[b] (8)	2578	22.0	11.2	27.6	39.2
Patek et al (69)	1-mo recall	w/o liver disease (69)	3544	51.4	8.1	N.A.	N.A.
		cirrhosis (195)	3394	54.9	5.9	N.A.	N.A.
Simko et al (84)	24-hr recall	w/o liver disease (20)	3135	24.2	9.5	N.A.	N.A.
		liver disease (62)	3093	34.6	8.4	N.A.	N.A.

[a]Clinically severe.
[b]18% had liver disease defined by prolonged BSP retention.

or fatty liver alone and patients who had cirrhosis without alcoholic hepatitis. In this study, complete nutritional assessment was performed in 284 patients. These patients were compared with a group of alcoholics matched for age and alcohol consumption, but without clinically evident liver disease. None of the patients with liver disease was completely free from malnutrition, although some indicators of malnutrition (e.g. decreased serum albumin) could arise from liver disease alone. In 62% of alcoholics without liver disease, one or more signs of malnutrition were present.

Alcohol consumption averaged 220 g/day and was similar in patients with and without liver disease. The amount of alcohol consumption did not correlate with the severity of liver disease. However, an inverse relationship was noted between nonalcoholic calorie consumption and the severity of liver disease. Nonalcoholic calorie consumption decreased from 2176 kcal in alcoholic patients without liver disease to 2015 kcal in patients with mild alcoholic hepatitis to 1552 kcal in patients with severe alcoholic hepatitis.

Despite this reduction in nonalcoholic calorie consumption, the mean consumption of protein exceeded 50 g/day, even in patients with severe alcoholic hepatitis. Similar results have been obtained in other dietary surveys comparing protein intake in alcoholics with and without serious liver disease. In several studies, protein intake was significantly lower in cirrhotics compared to alcoholics without liver disease. These results are summarized in Table 3. When expressed as grams per day, the protein intake was above the Recommended Dietary Allowance in most patients. Although dietary protein intake might be adequate, it is possible that protein requirements are increased in alcoholics. Factors that could contribute to malnutrition despite adequate dietary protein intake include malabsorption (59, 60) and azotorrhea (75), inhibition of protein synthesis by alcohol or acetaldehyde (24), and increased urinary excretion of nitrogen (57). Increased hepatic oxygen consumption, which may occur after chronic ethanol ingestion, is associated with increased protein degradation (41).

Nutritional deficiencies are common in alcoholics even in the absence of liver disease. However, these deficits were most severe in those patients with the most clinically severe liver disease (58). Furthermore, the clinical severity of liver disease is better correlated with nutritional parameters than with morphological changes seen on liver biopsy (28). In patients with moderately severe alcoholic hepatitis, Diehl and coworkers (28) found that patients consumed more calories per basal energy expenditure (BEE) than necessary to maintain weight, and met expected standards for protein intake as well. These patients were in the 99th percentile for ideal body weight. However, the following indicators of nutrition were uniformally suboptimal: creatinine-height index; arm muscle area; arm fat area; hematocrit; and plasma levels of short half-life visceral proteins (such as retinol binding protein), prealbumin, and longer half-life proteins (such as albumin) (28). These findings imply that patients with active alcoholic liver disease are unable to utilize dietary protein efficiently. In addition, alcohol itself may be an ineffective source of energy during times of high alcohol consumption, as mentioned earlier.

The prevalence of malnutrition in patients with advanced alcoholic disease has lead to several trials of specific nutritional therapy in patients with alcoholic hepatitis. Nasrallah & Galambos (66) reported decreased mortality from acute alcoholic hepatitis in patients receiving parenteral amino acid supplementation. In this study, patients received 51.6 g of protein as an amino acid infusion in addition to a high-calorie, high-protein diet. Significant reduction in mortality and improvement in biochemical parameters of liver function were observed in the treated group compared with controls. In a randomized controlled trial of parenteral amino acid therapy in 15 patients with biopsy-proven alcoholic hepatitis, Diehl and coworkers (28) found that parenteral amino acid therapy improved the clinical severity of liver disease more rapidly but, at the end of 30 days, was no more beneficial than standard therapy in improving creatinine-height index, arm muscle area, arm fat area, and plasma proteins. Amino acid treatment resulted in greater resolution of fat infiltration but did not otherwise affect hepatic histology. Thus, improvement in protein nutrition had more effect on the clinical than on the histological index of severity of liver disease.

Nutritional deficiencies, resulting from either decreased intake or increased nutritient requirements, are best correlated with clinical rather than histological severity of alcoholic liver disease (17, 28, 58). Certainly the daily amount of alcohol ingested and the duration of excessive drinking are the two most important determinants of the risk of developing serious alcoholic liver injury. Furthermore, cirrhosis can and does occur even in well-nourished individuals. Current evidence suggests that liver disease in alcoholics is not a result of malnutrition independent of the effects of alcohol, but the close relationship between clinical severity of liver disease and nutritional deficiencies, coupled with evidence that nutritional therapy is beneficial in improving the rate of recovery from alcoholic liver disease, suggests a definite role for nutritional parameters in modulating the course of alcoholic liver disease.

SUMMARY

Alcoholic beverages contribute an appreciable percentage (4–6%) to the total caloric intake in Western societies. The caloric value of ethanol as fuel may be dose-related. Most evidence suggests that at moderate intake levels of less than 45 g/day (3 drinks) ethanol is efficiently utilized as a fuel by the liver. At high intakes, ethanol calories may not be utilized for cellular synthesis of ATP and maintenance of weight. The exact mechanism for this inefficient utilization remains unknown but may be related, in part, to metabolism of ethanol by the microsomal ethanol-oxidizing system, a reaction that does not contribute to generation of reducing equivalents for ATP synthesis.

Although ethanol is utilized for ATP synthesis after single-dose administration, chronic consumption leads to morphological changes in hepatic mitochondria and to decreased ATP synthesis. Reductions in the activities of the enzymes of the mitochondrial electron transport chain have been reported after alcohol feeding and may help to explain decreases in hepatic ATP synthesis. There is some evidence that ATP degradation by "Na-K ATPase" is increased after ethanol feeding and that hepatic O_2 consumption is likewise enhanced. However, other studies have failed to demonstrate enhanced O_2 consumption.

Current evidence suggests that malnutrition alone is not sufficient to explain the pathogenesis of chronic liver disease in alcoholics. Although the daily amount of alcohol consumed and the duration of excessive consumption are clearly important factors in the development of alcoholic hepatitis and cirrhosis, other factors, particularly nutritional deficiencies, may modulate the risk of developing alcohol-related liver damage. The prevalence of malnutrition is exceedingly high in alcoholics with clinically severe liver disease. Nutritional deficiencies are better correlated with a clinical index of severity than with histologic severity of alcoholic hepatitis. Prognosis and outcome of patients with alcoholic liver disease may be affected by nutritional deficiencies, which thus provides a rationale for aggressive nutritional management of these patients.

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