Learning Objectives

- To understand the metabolic problems of patients who have abused alcohol;
- To know the causes of malnutrition in patients who have abused alcohol;
- To identify specific nutritional deficiencies in patients who have abused alcohol;
- To know the specific risk of thiamine deficiency in patients who have abused alcohol;
- To learn the best approaches to nutritional support in patients who have abused alcohol.

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Key Messages

- A threshold dose above which alcohol starts to have detrimental effects on nutrition is difficult to determine;
- Many alcoholics are malnourished, either because they consume too few essential nutrients or because alcohol disturbs the proper absorption, digestion, and use of those nutrients;
- Many alcoholics who are hospitalized for medical complications of alcoholism experience severe malnutrition.

1. Introduction

Alcohol is one of the most attractive recreational drugs worldwide along with coffee and tea. Misuse of alcohol undoubtedly induces pathological changes in most organs of the body. Many alcoholics are malnourished, because they consume too few of the essential nutrients: protein, lipid, carbohydrate, vitamins, and trace elements, and/or because alcohol impairs proper digestion and absorption. Alcohol affects both energy supply and maintenance of structure. It interferes with the nutritional process by affecting digestion, absorption, metabolism and excretion of nutrients. The term alcoholism was introduced by Magnus Huss in 1849. The usage of term “alcoholism” as a diagnostic entity fell out of disfavor with the World Health Organisation, which prefers the category of “alcohol dependence syndrome” (1). This is characterized by uncontrolled and compulsive consumption of alcohol despite its negative effects on health, relationships and social position. Alcoholism is defined as a treatable disease, as are other drug addictions.

Alcohol consumption has been identified as a component cause of more than 200 health conditions covered by the ICD-10 disease and injury codes. Also, it is important to underline that alcohol consumption can contribute to more than one type of disease or injury in the drinker. Overall, in 2012, about 3.3 million deaths were estimated to have been caused by alcohol consumption. This corresponds to 5.9% of all deaths, or one in every twenty deaths in the world (7.6% for men, 4.0% for women). This is greater than, for example, the proportion of deaths from HIV/AIDS (2.8%), violence (0.9%) or tuberculosis (1.7%). In 2012, 5.1% of the global burden of disease and injury, as measured in disability-adjusted life years
(DALYs) was attributable to alcohol. Between 4% and 25% of the worldwide disease burden due to specific cancers can be attributed to alcohol. Alcohol consumption contributes about 10% of the disease burden due to tuberculosis, epilepsy, haemorrhagic stroke and hypertensive heart disease, as well as an immediately obvious contribution of alcohol liver disease to the global burden of disease (2).

Alcohol abuse is associated with primary malnutrition (3), whereas secondary malnutrition may also occur because of interference with the digestion, absorption, and metabolism, of vitamins such as folate, thiamine, and vitamin A (4). The reported prevalence of malnutrition in these patient populations probably underestimates the prevalence of nutritional risk factors and micronutrient undernutrition. Multiple tools assessing malnutrition, appetite, quality of diet, and blood tests have different advantages and can identify further the needs and appropriateness of nutritional education in patients during treatment for alcohol use (5). Malnutrition has been more frequently reported among “skid-row” and lower-class alcoholics than in middle-class ones. In one study, only 8% of alcoholics of middle and high socioeconomic status were malnourished, in contrast with 32% of those belonging to a low social class (6). Irregular feeding and loneliness may be the link between social and family problems and malnutrition.

1.1. Alcohol Absorption

Alcohol interferes with the process of nutrition by affecting digestion, absorption, metabolism and excretion of nutrients. Alcohol inhibits the digestion of food by decreased secretion of digestive enzymes from the pancreas (7). Alcohol has a direct harmful effect on the cells lining the stomach and intestine, thus disabling transport of some nutrients into the blood (8). Alcohol absorption in the stomach is, however, low. Absorption occurs by flow across the mucosal concentration gradient at all sites in the GI tract; it is fastest in the duodenum and jejunum and decreases more distally. The endogenous microbiota of the GI tract can also metabolize dietary carbohydrates into a mixture of alcohols including ethanol. Alcohol is absorbed by passive diffusion across concentration gradient (alcohol is much higher in the lumen) across the cell membranes of the mucosa, submucosal space and then into the submucosal capillaries. After ingestion, it can be detected in the blood within 5 minutes. A
A dose of 0.8 g ethanol/kg body weight (56 g ethanol consumed by a 70 kg male) will typically result in a blood ethanol concentration of 100–200 mg/dl (22–43 mmol/l) between 15 and 120 minutes after dosage. The highest concentrations occur after 30–90 minutes. Rapid alcohol consumption leads to higher concentration in the stomach and small intestine, leading to faster absorption. Food delays gastric emptying into the duodenum, and ameliorates the sharp rise in blood ethanol concentration (BEC) found when alcohol is taken on an empty stomach (Fig. 2). Food also increases elimination of ethanol from the blood. The caloric value of the meal appears more important than the precise balance of nutrients.

![Fig.2 Blood ethanol concentration after oral intake of ethanol. A subject is given 0.8 g/kg ethanol over 30 minutes either after an overnight fast or after breakfast. The peak of the concentration of ethanol in blood and the area under the curve are reduced if ethanol is consumed with food. Source: Encyclopedia of Human Nutrition, Second Edition. 2005](image)

1.2. Metabolism of Alcohol

Most absorbed ethanol is metabolized in the liver. Gastric metabolism accounts for approximately 5% of ethanol oxidation and 2–10% is excreted in the breath, sweat, or urine. Generally, alcohol is initially oxidized to acetaldehyde, and then to acetate. Acetate is partly metabolized to acetyl-CoA which can, in turn, be metabolized in the brain, muscle, and kidney. In the liver alcohol is metabolized by various enzyme systems:

1. Alcohol dehydrogenase (ADH), is a ubiquitous cytosolic intracellular enzyme. In subjects, consuming alcohol at moderate levels or only occasionally, most alcohol is broken down by ADH. ADH converts ethanol to acetaldehyde, a toxic and highly reactive molecule. During this reaction, hydrogen is removed from the ethanol and transferred to nicotinamide adenine dinucleotide (NAD), converting it to reduced NAD (NADH). NADH participates in many other metabolic reactions, transferring on the hydrogen to other compounds. The excess cellular NADH has potentially harmful effects on the cells, and subsequently, the acetaldehyde is converted to acetate by aldehyde dehydrogenase.
There are several classes of alcohol dehydrogenase isoenzymes (9): liver (ADH1-4,6,7), lung (ADH2), stomach (ADH3,6,7), cornea (ADH4), oesophagus (ADH1-7), most other tissues (ADH5);

2. The microsomal ethanol-oxidizing system (MEOS) an enzymatic sequence that occurs in microsomes split off from the endoplasmic reticulum;
3. The catalase enzymes— peroxisome-based process;

Fig. 3 Oxidative pathways of alcohol metabolism (64)

1.3. Pathways of Alcohol Metabolism

The MEOS plays an important role in alcohol metabolism, particularly after higher amounts of alcohol consumption. The enzyme cytochrome P450 is the main component of the MEOS. Like ADH, it converts alcohol to acetaldehyde. This reaction also relies on oxygen and reduced nicotinamide adenine dinucleotide phosphate (NADPH), resulting in the production of NADP and water. Highly reactive, oxygen-containing molecules - oxygen radicals or reactive oxygen species (ROS) - are produced. These ROS can contribute to liver damage by a variety of mechanisms. The rate of ADH break down of alcohol generally, stays the same. However, the activity of the MEOS could be increased (induced) by alcohol consumption. MEOS metabolizes not only alcohol but other compounds as well; that is why enhanced MEOS activity because of high consumption of alcohol also can alter the metabolism of medications. It could contribute to harmful interactions between alcohol and those medications or otherwise influence their activity (10).

The ADH pathway requires reduction of NAD to NADH+H, but MEOS requires oxidation of NADPH to NADP, a process that consumes ATP and dissipates heat. Therefore, the ADH pathway yields 16 mol ATP/mol of ethanol oxidized, whereas MEOS yields only 10. The MEOS pathway scarcely works in occasional ethanol consumers but is induced in chronic alcoholics (11). CYP 2E1 is the most important variant of the cytochrome P 450 in alcohol metabolism. The activity of this molecule can increase up to fourfold following alcohol consumption.
Cytochromes P450, such as CYP1A2 and CYP3A4, are also involved in the breakdown of alcohol (10). Cytochrome P450 2E1 (CYP2E1) is up-regulated in the condition of chronic alcohol abuse. It assists ADH in converting alcohol to acetaldehyde. ROS, such as superoxide ions and hydrogen peroxide, generated by the CYP2E1 isoenzyme are responsible for the pro-inflammatory profile of the alcohol liver injury by:

1) activation of redox-sensitive transcription factors [e.g., nuclear factor kappa B (NF-κB)];
2) recruitment of neutrophils and other immune cells;
3) an increase in the level of circulating pro-inflammatory cytokines;
4) contribution to the peroxidation of lipids associated with alcoholic liver injury (12).

1.4. Microsomal Ethanol Oxidizing System

Chronic consumption of alcohol increases the rate of clearance of ethanol from the blood, mainly by MEOS in the liver. The main enzyme of the MEOS is cytochrome P4502E1 (CYP2E1). CYP2E1 is highly inducible by alcohol. The Km for ethanol for CYP2E1 is much higher than for liver ADH, ranging from 8–10 mmol/l, meaning that alcohol is involved in the MEOS only at a high cellular concentration. CYP2E1 is important in alcohol clearance at higher consumption levels. - CYP2E1 is capable of producing active oxygen species: superoxide anions, hydroxyl radicals, and hydrogen peroxides. CYP2E1 is rather a "leaky" enzyme. The production of oxyradicals creates a basis for the higher capacity for CYP2E1 to initiate NADPH-dependent lipid peroxidation (13). It was demonstrated that CYP2E1 is a major microsomal source of hydrogen peroxide and NADPH-dependent lipid peroxidation. Model experiments in liver cell lines that overexpress CYP2E1 confirm that there is a direct link between the pro-oxidants production in the microsomal pathways and cellular injury. The role of CYP2E1 in ROS and lipid peroxides production was shown in the experiments with specific inhibitors of CYP2E1, which provided protection against cytotoxicity. These products can interfere with the normal metabolism of other nutrients, particularly lipids, and contribute to liver cell damage. In alcoholic liver disease hepatic CYP2E1 activity decreases within days of alcohol cessation. However, CYP2E1 is continuously increased in the livers of patients with non-alcoholic steatosis (NASH) (14). Peroxisomal catalase is of little significance in the metabolism of ethanol.

1.5. Metabolism of Acetaldehyde

Acetaldehyde is highly toxic; it is rapidly converted to acetate by aldehyde dehydrogenase (ALDH) (Fig. 3). The presence of ALDH in tissues reduces the toxic effects of acetaldehyde. There are two isoforms of ALDH: 1) Cytosolic ALDH1 – distributed in many tissues; 2) Mitochondrial ALDH2 present in all tissues except red blood cells. At a higher level, the enzyme is present in liver, kidney, muscle and heart (15). In alcohol abusers, alcohol oxidation is increased through induction of MEOS, but the capacity of mitochondria to oxidize acetaldehyde is diminished. That is why the hepatic acetaldehyde increases with chronic ethanol consumption.
1.6. Metabolism of Acetate

The absorbed ethanol is mainly metabolized in the liver and released as acetate, which is increased more than twice after ethanol consumption. Acetate easily crosses the blood–brain barrier and is actively metabolized in the brain. Both cardiac and skeletal muscle are very important in the metabolism of acetate. It can also be converted into acetyl-CoA via a reaction catalysed by Acetyl-CoA synthetase. The reaction requires ATP. Acetyl-CoA enters Kreb’s cycle for energy production. In cholinergic neurons, acetylcholine is produced from acetyl-CoA. Acetyl-CoA is the substrate for lipid synthesis, particularly in the fed state. A breakdown of alcohol in the liver, both by the enzyme alcohol dehydrogenase and by a microsomal ethanol-oxidizing system (MEOS), generates toxic acetaldehyde and highly reactive oxygen species, interfering with the normal metabolism of nutrients, particularly lipids, and can contribute to liver cell damage. Nutritional approaches can help to prevent or ameliorate alcoholic liver disease (16).

1.7. Malnutrition and Alcohol

Ethanol accounts for up to 10% of the total energy intake among social drinkers, this proportion reaching more than 50% in some alcoholics. Because of ethanol’s high caloric content (7.1 kcal/g), ethanol consumption has been considered a risk factor for weight gain and obesity (17). However, weight loss is common among heavy drinkers, and there is controversy regarding changes in body weight and moderate alcohol consumption. From a nutritional point of view, ethanol is an energetic compound but lacks any other nutritional value (18). Many of the abnormalities in the absorption reverse when alcoholics are provided a nutritious diet, even in the case of continued intake of alcohol (19). It is well established that fasting reduces the liver content of ADH (units per liver) (20). Crabb et al. found that the reduction in enzyme activity was paralleled by a reduction in alcohol elimination rate. Bosron’s laboratory measured the effect of 72 h of fasting on rat liver ADH. The study showed that the synthetic rate fell during fasting, and the degradation rate increased substantially. Surprisingly, refeeding or meal feeding the rats a high carbohydrate, fat-free diet resulted in a reduction in total ADH activity in the liver, suggesting that fat content of the diet could contribute to the expression of ADH.

2. Shift of Nutrients

Moderate ethanol consumption increases rather than decreases dietary intake. In contrast, advanced alcoholism leads to a substantial reduction of dietary intake, so consumption of other nutrients progressively decreases as ethanol intake increases (21). Although the diet of a heavy drinker matches or even surpasses the caloric requirements, it may be inadequate regarding protein, essential lipid, and other nutrient consumption. Alcohol consumption, particularly in heavy drinkers, influences the drinker’s diet and also affects the metabolism of those consumed nutrients. That is why, even when the drinker consumes a sufficient quantity of proteins, fats, vitamins, and microelements, deficiencies could be developed if those nutrients are not properly absorbed from the gastrointestinal tract into the blood, are not digested effectively, and are not used adequately by the body. The main problems are related to proteins and vitamins (10). In addition, ethanol may cause satiety because it delays gastric emptying. There is controversy about the effect of ethanol on leptin secretion - whereas acute
ethanol intake in healthy volunteers reduces serum leptin levels, these are increased in advanced alcoholics with dependence and decreased in alcoholics admitted for organic complications (22).

3. Ethanol-Induced Caloric Wastage

Overall, the wide range in nutritional status in alcohol abusers reflects, at least in part, the proportion of total ingested calories in the form of alcohol and the differences in consumed food. Moderate alcohol intake is defined from when alcohol accounts for about 16 percent of total calories (roughly 320 kcal in a 2,000-kcal diet) (10). It is associated with slightly increased total energy intake. At moderate alcohol consumption, and even at higher drinking levels (up to 23 percent of total calories), drinkers typically substitute alcohol for carbohydrates in the diet. When drinkers consume more than 30 percent of their total calories in the form of alcohol, they also significantly reduce protein and fat intake as well as carbohydrate. These drinkers’ consumption of vitamin A, vitamin C, and thiamine (vitamin B1) also may fall below the recommended daily allowances (10). Pirola and Lieber (1972) in classic studies found a weight loss of about 1 kg after consumption for 14 days of a diet in which 50% of calories were substituted by ethanol. Moreover, no significant weight gain was observed when 2000 kcal (in the form of ethanol) were added to the diet, whereas subjects experienced a weight gain of nearly 3 kg when the same amount of calories was consumed in the form of chocolate (23).

4. Increased Energy Expenditure

The effect of alcohol on body weight is dependent on the amount of consumed alcohol and timing in relation to meals as well as on the presence of organ damage, in particular, alcoholic liver disease (24). In healthy volunteers, short-term ethanol administered as 25% of the total energy requirements, either added to the diet or given instead of other food, increased energy expenditure (24). Since this experiment was carried out in healthy non-drinkers, ethanol should have been mainly metabolized by the ADH system and not by the MEOS (24). Therefore, mechanisms other than MEOS must be involved in the alcohol-mediated increase in energy expenditure, such as acetaldehyde-induced catecholamine secretion.

Levine et al. (25) also showed increased fat oxidation and an increased REE, which are related to ethanol ingestion since both decrease within 4 days after withdrawal. Thus, it seems that ethanol increases REE, not only due to an enhanced MEOS metabolism but also due to increased catecholamine secretion and uncoupled oxidative phosphorylation due to mitochondrial damage. Whereas body weight is usually unaffected by moderate alcohol consumption in healthy subjects, chronic alcoholics who substitute alcohol for other nutrients lose weight due to the energy neutral effect of alcohol in the diet. Heavy drinkers (mean consumption of 195 g ethanol/d) when compared with social drinkers, show a significantly lower weight due to lower fat mass and increased fat oxidation (26). Thus, it seems that ethanol increases REE, not only due to an enhanced MEOS metabolism but also due to increased catecholamine secretion and uncoupled oxidative phosphorylation due to mitochondrial damage (27). Moderate drinkers on regimens of weight loss are less likely to lose body weight when consuming alcohol with the meals since one of the effects of alcohol is to decrease restraint over food intake. However, if alcohol is consumed with high-fat meals
the subjects are more likely to gain weight due to a strong positive effect of alcohol on fat storage and negative effect on the oxidation of fat.

5. Effect of Ethanol on Fat Oxidation

Ethanol may inhibit fat mobilization due to the antilipolytic effect of acetate (28). In addition, an increased NADH/NAD ratio may enhance liver fatty acid and triglyceride synthesis. Consumption of 96 g ethanol in healthy non-alcoholic individuals (about 25% of the daily caloric requirement) reduced the lipid oxidation rate by about 30%, an effect which was only observed during the period of the day in which ethanol was consumed and metabolized (29). No significant effect was observed on protein and carbohydrate metabolism. The intake of 24 g of ethanol by eight healthy volunteers led to an increase in hepatic de novo lipogenesis (from 2 to 30%). The release of non-esterified fatty acids by adipose tissue decreased by 53%, and whole lipid oxidation by 73%. Therefore, the liver metabolizes ethanol into acetate, and this major end product of ethanol inhibits lipolysis (30). These changes would theoretically favour lipid accumulation and weight gain. However, epidemiological studies support the conclusion that moderate ethanol consumers (less than 50 g/d), despite an increase in the total energy intake, show weight loss (31). This apparent paradox — the loss of weight in moderate drinkers — has been interpreted as due to an ethanol-induced increased muscle sensitivity to insulin and a down-regulation of insulin effect on adipose tissue, decreasing fat mass (32). Addolorato et al. (1998) (26), in chronic heavy drinkers (195 g/d) without liver cirrhosis or malabsorption, found a lower body weight due to fat mass reduction (the triceps skinfold was reduced), and a preferential use of lipids as fuel when compared with social drinkers. Fat distribution was also different in heavy drinkers compared to social drinkers. Heavy drinkers showed a raised waist-to-hip ratio (both in men and women), a pattern which has been related to visceral fat deposition and liver steatosis, even in non-alcoholic subjects. These metabolic changes improved one month after withdrawal and totally reversed three months after alcohol cessation (26).

6. Effects of Ethanol on Carbohydrates Metabolism

Alcohol can impair the mechanisms of control of blood glucose levels, resulting in either increased or decreased blood glucose even in the case of adequate intake of food. In non-diabetic alcoholics hyperglycaemia is usually temporary and without consequence. Hypoglycaemia can occur when a fasting or malnourished person consumes alcohol and cause serious injury even if this condition is short-lived. When there is no food supply, stored sugar in the form of glycogen is depleted. In this situation the products of alcohol metabolism inhibit gluconeogenesis, the process of formation of glucose from other compounds such as amino acids (33).

7. Effects of Ethanol on Protein Metabolism

Ethanol increases urinary nitrogen excretion (34). Ethanol administered to rats leads to reduced protein synthesis and type II muscle fibre atrophy, an effect probably dependent more on acetaldehyde than on ethanol itself. Type IIb fibre atrophy is more intense when a low-protein diet is added to the ethanol (35). It has been clearly shown that ethanol leads to muscle atrophy and cardiomyopathy in the absence of any nutritional impairment (36). In
addition to muscle protein, ethanol and acetaldehyde may alter protein synthesis in every body tissue. It decreases protein synthesis in the majority of the tissues, (such as bone and liver) and causes negative whole-body nitrogen balance; it also increases liver collagen synthesis (37).

Liver enlargement, hepatomegaly is a common finding in alcoholics and experimental alcohol-fed animals. Increased liver mass arises from the accumulation of proteins and lipids (38).

Protein gain/accumulation in alcohol-induced fatty liver likely contributes to the more severe alcohol-induced liver pathologies. The accumulated proteins could be damaged by reactive oxygen species and other hazardous molecules generated by ethanol metabolism, from leakage of damaged mitochondria, and from ethanol-induced secondary reactions in which oxidants are generated (39). The activity of protein synthesis in livers of chronically ethanol-fed rats is normal. But the rate of hepatic protein degradation in ethanol-fed animals declines by 36-40% (40).

Ethanol administration reduces the proteolytic capacity of lysosomes and disturbs the degradation of proteins with half-lives greater than eight hours, which are mainly degraded in lysosomes. The proteolytic capacity in liver lysosomes is reduced through lowering of the content of cathepsin (41). These changes in lysosomes likely influence the autophagosome degradation in the autophagy process (42). These data lead to the suggestion that ethanol consumption suppresses autophagy (43). Significant cellular toxicity and the impairment of protein synthesis and degradation take place in alcohol-exposed liver cells, along with the changes in energy balance and responses to pathogens.

Alcohol can interfere with the uptake of essential amino acids. In experimental studies, it was found that animals absorbed fewer amino acids from the intestine after the intake of alcohol (44). Patients with chronic liver failure also exhibit some of these defects in protein metabolism. These include a diminished production of blood proteins in the liver (albumin, globulins and blood clotting factors), decreased synthesis of urea, and a decreased metabolism of aromatic amino acids. The consequences of these defects have an important clinical impact:

- Decreased production of the blood proteins, particularly albumin, may lead to hypoalbuminaemia and as consequence changes in the blood volume as well as the concentrations of metabolites and minerals. Excessively low albumin levels may cause or exacerbate ascites in patients with cirrhosis, which may worsen the impaired blood flow in the patient’s damaged liver.

- Reduced levels of blood-clotting factors could predispose to the risk of internal bleeding in the gastrointestinal tract, which can have serious health consequences.

- Reduced urea production results in excessive ammonia; that could increase the likelihood of the development of altered brain function - hepatic encephalopathy.

- Abnormalities in the balance of amino acids in the blood, such as increased levels of aromatic amino acids, can also increase the risk of hepatic encephalopathy (10).
8. Secondary Malnutrition in Chronic Pancreatitis

Chronic pancreatitis and liver disease are the two main causes of secondary malnutrition in alcoholics. Moreover, alcoholics frequently suffer infections and injuries, leading to superimposed stress malnutrition (18). Chronic alcoholic pancreatitis severely impairs nutritional status when exocrine pancreatic failure and diabetes mellitus with hypoinsulinaemia (another cause of malnutrition) are present. Exocrine pancreatic dysfunction was found in 26% of 105 heavy drinkers (mean of 195 g/d) without any signs or symptoms of pancreatic alteration persisting 30 days after withdrawal. One-third of the affected cases initially had steatorrhoea (45). Chronic gastritis, with anorexia and vomiting, and diarrhoea, are common complications of alcohol consumption as well, contributing to poor nutritional status.

9. Secondary Malnutrition in Alcoholic Liver Disease

Although the biological mechanisms of alcoholic liver disease (ALD) is well established: oxidative stress with induction of cytochrome p450 2E1, rising of acetaldehyde, release of inflammatory cytokine, abnormal lipid metabolism and induction of apoptosis in hepatocyte, unfortunately there is no standard therapeutical approach for its prevention. Alcoholic liver disease results in changes in body composition and energy balance. According to large multicentre studies, alcoholic hepatitis patients demonstrate evidence of protein-calorie malnutrition, on the basis of muscle wasting and oedema, low albumin levels and low levels of visceral proteins, as well as decreased cell-mediated immunity. The 6-month mortality is related in part to the severity of malnutrition. Compensated liver cirrhosis may be associated with a normal or only slightly impaired nutritional status. In cirrhotics, interpretation of decreased serum albumin, transferrin, and prealbumin levels may be difficult since they may be secondary to liver failure rather than to malnutrition, or may even be related to infection or injury (46). Alcoholics with liver disease show some metabolic disturbances which may clearly influence nutritional status. A hypermetabolic state with increased thermogenesis has been observed in these patients, especially in those with superimposed alcoholic hepatitis (47). Furthermore, not all cirrhotics are hypermetabolic. In fact, Muller et al. (1992) report hypermetabolism in 18% and hypometabolism in 31% of their cirrhotics. Those who were hypermetabolic showed a reduced muscle mass, whereas those who were hypometabolic, an increased fat mass (48). Cirrhotics cannot store glycogen and show resistance to insulin, so glucose oxidation decreases and lipid oxidation increases in nearly all the patients (49).

Cirrhotics with ascites showed reduced lean and fat mass. Ascites causes anorexia and early satiety due to gastric compression and abdominal distension but not to altered gastric emptying: large volume paracentesis improves satiety and dietary intake but has no effect on gastric emptying (50). Anorexia is the main cause of weight loss in alcoholic liver disease, and may be initiated by higher circulating levels of leptin. Active alcoholic hepatitis contributes to raised resting energy expenditure and is another cause of weight loss. Resting energy expenditure is normal in stable cirrhotic alcohol abusers, who are also typically underweight or malnourished in part is due to the preferential metabolism of endogenous fat stores. At the same time, the digestion of dietary fat is decreased in cirrhotic patients due to diminished secretion of bile salts and pancreatic enzymes.
10. Ethanol Effect on Intestinal Permeability to Endotoxins

Alcohol intake can promote the growth of Gram-negative bacteria in the intestine and may result in accumulation of endotoxin. Metabolism of alcohol by Gram-negative bacteria and intestinal epithelial cells can lead to accumulation of acetaldehyde and increased intestinal permeability to endotoxin through a mechanism of increasing tyrosine phosphorylation of tight junction proteins. Increased permeability to endotoxin could be stimulated by alcohol induced generation of nitric oxide which by reacting with tubulin may cause damage to microtubule cytoskeleton and disruption of intestinal barrier function. Increased permeability in the intestine can lead to an increased transfer of endotoxin to the liver and the general circulation where endotoxin could initiate inflammatory changes. Alcohol may also increase the permeability of the intestine to peptidoglycan which can trigger an inflammatory response in the liver and other organs. Acute alcohol exposure may potentiate the effect on intestinal bacterial growth and permeability of burn injury.

When decreasing the number of Gram-negative bacteria in the intestine, it could result in decreased production of acetaldehyde and of endotoxin.

The intestinal permeability may be preserved by administering epidermal growth factor, L-glutamine, zinc or oats supplementation in this way preventing the transfer of endotoxin to the general circulation. A reduction of the number of intestinal Gram-negative bacteria and preserving intestinal permeability to endotoxin may attenuate alcoholic liver and other organ injuries (51).

11. Effects of Ethanol on Vitamins

Chronic heavy drinking is associated with many deficiencies of vitamins mainly because of decreased food ingestion, but also by impaired absorption, metabolism, and utilization. Alcohol inhibits fat absorption and thereby impairs absorption of the vitamins A, E, and D that are usually absorbed along with dietary fats. Fat-soluble vitamins A, D, E, K, and water soluble vitamins B and C are also deficient in some alcoholics (52). Deficiency of thiamine is usually associated with chronic alcoholism because it affects thiamine uptake and utilization. Alcohol alone can also decrease thiamine absorption by 50% in one-third of patients who are not malnourished (53).

11.1. Micronutrient Deficiencies

Chronic exposure to excessive amounts of ethanol is associated with deficiencies of micronutrients such as thiamine, folate, pyridoxine, vitamin A, vitamin D, and magnesium, zinc, and potassium. These deficiencies are increased in the presence of ALD, resulting in decreased numbers of hepatocytes for vitamin storage and metabolism. The clinical symptoms of ALD are related to vitamin deficiencies. are related to vitamin deficiencies.

11.2. Thiamine Deficiency

Deficits in circulating thiamine have been reported in 30–80% of alcoholic inpatients. Functional deficits in the activation of thiamine-dependent enzymes have been reported in 35% of alcoholics. Neuropathological brain lesions related to thiamine deficiency have been
reported in 12.5% of autopsy brain samples from alcoholics. Certain inherited differences in thiamine binding and utilization which may be exacerbated by alcoholism have been associated with an increased inherited vulnerability of thiamine deficiency in certain individuals (54). Low blood thiamine concentrations have been found in around 80% of patients with alcoholic cirrhosis. Thiamine is a precursor of a coenzyme in the metabolism of carbohydrates, in particular for pyruvate dehydrogenase (PDH) and transketolases (TK), which are important for aerobic metabolism particularly in heart and nerve tissue. Acute exposure to alcohol reduces the activity of intestinal transporters for thiamine absorption. The major neurological signs and symptoms are peripheral neuropathy, partial paresis of ocular muscles, cognitive defects, and severe memory loss. The presence of peripheral neuropathy is sometimes referred to as ‘dry beriberi,’ while the other symptoms constitute the Wernicke-Korsakoff syndrome.

Abnormal eye movements can be treated acutely with thiamine injections. However, the other signs are often permanent and contribute to the dementia that often troubles alcoholics after years of drinking. ‘Wet beriberi’ refers to the high-output cardiac failure that can also occur in thiamine-deficient alcoholics, and is responsive to thiamine therapy in addition to conventional treatment. Since endogenous thiamine is used during carbohydrate metabolism, acute cardiac failure can be precipitated by the administration of intravenous glucose to malnourished and marginally thiamine-deficient patients by depletion of remaining thiamine stores. This process can be prevented by the addition of soluble vitamins including thiamine to malnourished chronic alcoholic patients who are undergoing treatment for medical emergencies. Research in animal models has hypothesized that deficiency of certain vitamins B, particularly thiamine deficiency, may contribute directly to pathological drinking in acute alcoholics. Rats exposed to dietary thiamine depletion or treatment with thiamine antagonists show increased total alcohol consumption that was readily reversed after thiamine rescue. These findings in the studies with rats suggest that subclinical levels of thiamine deficiency could moderate the consumption of alcohol and that restoration of thiamine levels in blood could help to normalize drinking behaviours (54).

### 11.3. Folate Deficiency

Folates circulate in their dietary forms and in the methylated and reduced mono-glutamate form. Folates are necessary for amino acid and nucleotide metabolism, essential for DNA synthesis and play a central role in methionine metabolism. The consequences of folate deficiency include megaloblastic anaemia, elevated homocysteine in the blood, increased risk of neural tube defects in newborns, and altered cognition in the elderly. Before folate fortification in the US, the incidence of low serum folate levels in chronic alcoholics was at about 80%. Megaloblastic anaemia, due to the negative effects of folate deficiency on DNA synthesis, has been described in about one-third of patients with alcoholic liver disease. Excessive alcohol use is associated with reversible hyperhomocysteinaemia in chronic alcoholics because of the inhibitory effect of alcohol or its metabolite acetaldehyde on methionine synthase. Furthermore, folate deficiency may play a role in the pathogenesis of alcoholic liver disease. The causes of folate deficiency in chronic alcoholism are multiple. Except beer, all alcoholic beverages are devoid of folate, and the typical diet of the chronic alcoholic does not include its fresh vegetable sources. Chronic alcoholism is associated with intestinal folate malabsorption, decreased folate uptake by the liver, and accelerated folate
excretion in the urine. Alcoholic liver disease results in decreased liver stores of folate, so the duration of time for development of folate deficiency with marginal diet is shorter.

### 11.4. Pyridoxine Deficiency

Pyridoxine is the main cofactor in the metabolism of amino acids, including the elimination of homocysteine and production of neurotransmitters (GABA, dopamine). Much of the absorbed pyridoxine is taken up by the liver. In chronic alcoholism pyridoxine deficiency is caused by poor diet, and the displacement of pyridoxal phosphate from circulating albumin by acetaldehyde (alcohol metabolite) increases the urinary excretion. The serum levels of pyridoxal phosphate are commonly low in chronic alcoholics. The deficiency of pyridoxine is manifested by peripheral neuropathy and sideroblastic anaemia. The deficiency of pyridoxine is manifested by peripheral neuropathy and sideroblastic anaemia. In alcoholic hepatitis, the level of alanine transaminase (ALT) was found to be disproportionately low as compared to aspartate transaminase (AST), because of the need of pyridoxine for ALT activity (65).

### 11.5. Cyanocobalamin Deficiency

The intestinal absorption of vitamin B12 is decreased in chronic alcoholics due to defective uptake in the ileum. Lower levels of vitamin B12 in the liver may contribute to abnormal hepatic methionine metabolism with elevated serum homocysteine since this vitamin is a cofactor for methionine synthase. Serum levels of B12 are however often normal or increased due to the presence of B12 analogues in alcoholic liver disease.

### 11.6. Vitamin A Deficiency

Although serum levels of vitamin A are usually normal in chronic alcoholics, liver retinoids are progressively lowered through the stages of alcoholic liver disease. Vitamin A is stored as retinyl esters in fat-storing transitional Ito cells. The process of transformation of Ito cells to collagen-producing, hepatic stellate cells is associated with depletion of retinyl esters. The causes of vitamin A deficiency in alcoholic liver disease include malabsorption, which is due to decreased secretion of bile and pancreatic enzymes necessary for the digestion of dietary retinyl esters and their incorporation into water-soluble micelles prior to intestinal transport. The transport of retinol is impaired due to decreased hepatic production of retinol-binding protein. The metabolism of alcohol induces microsomal enzymes that promote the production of polar retinol metabolites, which are more easily excreted in the bile. The signs of vitamin A deficiency include night blindness with increased risk of automobile accidents and increased risk of oesophageal cancer. Patients with ALD are more susceptible to vitamin A hepatotoxicity so that supplemental doses should be used with caution. Depleted liver retinoid content may be a factor in hepatocellular carcinoma development in alcoholics. It is not only an increased risk of liver cancer that has been associated with alcoholism; alcohol consumption is also associated with increased rates of several types of cancer in addition to hepatocellular carcinoma, including cancer of the upper aerodigestive tract, colorectal cancer, and female breast cancer. Furthermore, some of these cancers have been linked with changes in retinoid homeostasis, such as tracheal squamous metaplasia (55).
11.7. **Vitamin D and Calcium Deficiency**

Chronic alcoholic patients are at increased risk for metabolic bone disease due to low vitamin D and hence decreased absorption of calcium. Alcoholic liver disease reduces the level of metabolism of Vitamin D to more active compounds, and reduces its absorption because of the decreased excretion of bile, poor diet, and often decreased sun exposure. Calcium deficiency results from low levels of vitamin D, and also because of the fat malabsorption that often accompanies alcoholic liver disease which results in increased binding of calcium to unabsorbed intestinal fatty acids.

12. **Effects of Ethanol on Minerals**

Deficiencies in minerals such as calcium, magnesium, iron, and zinc are common in alcohol abusers, although alcohol itself does not affect the absorption of these minerals (56). Rather, deficiencies seem to be secondary to other alcohol-related problems: decreased calcium absorption due to fat malabsorption; magnesium deficiency due to decreased intake, vomiting, and diarrhoea and increased urinary excretion, (57); iron deficiency due to gastrointestinal bleeding; and zinc malabsorption or losses in related to other nutrient deficiencies (56).

12.1. **Zinc Deficiency**

Zinc is a cofactor of certain enzymes, including retinol dehydrogenase, is stored in the pancreas, and circulates in the blood bound mainly to albumin. Chronic alcoholic patients are frequently zinc deficient because of poor diet, increased urine excretion (their low albumin rendering total serum zinc lower still). The consequences of zinc deficiency include night blindness from decreased production of retinal, decreased taste, and hypogonadism, which may result in lowered testosterone levels and increased risk of osteoporosis in men. Since zinc is required for cellular immunity, its deficiency may contribute to increased infection risk in alcoholic patients.

12.2. **Iron Deficiency**

Chronic alcoholic patients are often deficient in iron because of increased frequency of gastrointestinal bleeding, typically due to alcoholic gastritis or oesophageal tears from frequent retching and vomiting, or from rupture of oesophageal variates in patients with cirrhosis and portal hypertension. The main consequence of iron deficiency is anaemia, which may be aggravated by the concurrent effects of deficiencies of folate and pyridoxine. Conversely, increased iron exposure increases the risk and severity of alcoholic liver disease, because the presence of iron in the liver promotes oxidative liver damage during the metabolism of alcohol. Active alcoholism is associated with increased alcoholic liver disease activity. The relation between alcoholic liver disease and iron overload is well known (58). Necroinflammation, liver iron concentration, and ferritin were significantly higher in drinkers (59).

12.3. **Magnesium Deficiency**

A low level of magnesium is a common electrolyte disturbance in alcoholics. The mechanisms could include, increased transfer of magnesium from the extracellular space to intracellular fluid due to respiratory alkalosis, alcohol withdrawal syndrome and excess catecholamine
release, as well as increased gastrointestinal loss due to a chronic diarrhoea syndrome. Increased magnesium excretion could be another reason of hypomagnesaemia. Respiratory alkalosis from hyperventilation during alcohol withdrawal and malnutrition from decreased magnesium intake could contribute as well. During alcohol withdrawal hypomagnesaemia was observed in 29.8% of patients (60). Hypomagnesaemia patients more frequently had other acid-base and electrolyte abnormalities, such as hypophosphataemia, hypokalaemia, hypocalcemia, and respiratory alkalosis, than normomagnesaemic patients. Moreover, in hypomagnesaemic patients, magnesium levels in serum correlated with indicators of potassium and phosphorus excretion, suggesting that serum levels of magnesium play a central role in the homeostasis of the other electrolytes. Hypomagnesaemia is the most common electrolyte deficiency observed in alcoholic patients (61).

12.4. Potassium Deficiency

Patients with hypokalaemia had established hypomagnesaemia and respiratory alkalosis more commonly than normokalaemic ones. Hypokalaemia is a relatively common electrolyte abnormality observed in alcoholic patients. Inappropriate kaliuresis because of the co-existent hypomagnesaemia predominates (62).

12.5. Phosphate Deficiency

About 50% of alcoholics who are hospitalized have hypophosphataemia (29, 34). The alcoholic patient after admission to the hospital is prone to severe hypophosphataemia resulting from redistribution of extracellular phosphate into the cells. This intracellular shift can be mediated by one or both of two mechanisms: the release of insulin induced by the administration of dextrose-containing fluid and refeeding, and acute respiratory alkalosis. The major causes of chronic phosphate depletion in the alcoholic patient include poor dietary intake of phosphate and vitamin D; binding of dietary phosphates by antacid drugs used to treat recurring gastritis; chronic diarrhoea; and increased urinary phosphate excretion, which can result from secondary hyperparathyroidism induced by vitamin D deficiency and/or a proximal tubular defect associated with alcohol abuse. Even if alcoholic patients are not overtly symptomatic, they may have myopathy and weakness that are not clinically apparent (63).
13. References

15. Alcohol breakdown in the liver, both by the enzyme alcohol dehydrogenase and by microsomal ethanol-oxidizing system (MEOS), generates toxic products such as acetaldehyde.


