

# Psychiatric Implications of Nutritional Deficiencies in Alcoholism

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## Abstract

Malnutrition is common in chronic alcoholics. Hypocalcemia, hyponatremia, hypokalemia and hypophosphatemia have all been associated with chronic alcoholism. Alcohol intake is also associated with low serum magnesium, selenium and zinc levels. Water-soluble vitamins, such as vitamin B<sub>1</sub>, B<sub>2</sub>, B<sub>3</sub>, B<sub>6</sub>, B<sub>9</sub> and C, and fat-soluble vitamins, such as vitamin A, D, E and K have also been reported to be deficient in alcoholics. General causes of malnutrition in alcoholics are inadequate nutrient, particularly lack of water-soluble vitamins in their diet, reduced uptake, impaired utilization, increased requirements of nutrients and genetic predisposition to nutrient deficiency. Nutrient deficiencies are, therefore, a virtually inevitable consequence of alcohol abuse, not only because alcohol displaces food, but also because alcohol directly interferes with the body's use of nutrients, making them ineffective even if they are present. Chronic alcoholics exhibit a number of neurological disorders which are related to nutritional deficiencies, in particular vitamin deficiencies that are essential for normal cerebral functioning. Specific vitamin and nutrient deficiencies arising in chronic alcoholics may result in severe functional

impairment and tissue damage, mainly neuronal and vascular, in the brain. Nutritional deficiency in alcoholics also causes neurotransmitter dysfunction, ion channel dysfunction, oxidative stress and metabolic dysfunction in the brain. Nutritional deficiency in chronic alcoholics frequently leads to a mild to moderate cognitive impairment, including impairment in perceptual-motor skills, visual-spatial functions, learning/memory, and abstraction and problem solving. There are a number of nutritional deficiencies which need to be cared for but magnesium, thiamine, and other B vitamins need to be administered immediately. Nutritional therapy can aid in the recovery from alcoholism. Patients who have received nutritional therapy reported significantly less alcohol craving as well as significantly greater nutrient intakes, and a greater number abstained from alcohol. Although abstinence and proper nutrition remain the cornerstones of treatment, pharmacological modification of neurotransmitter function and/or enhancement of cerebral metabolism combined with behavioral methods may also be beneficial.

**Key words:** Alcoholism, Nutrition, Deficiency, Neuropathology, Neurophysiology, Neuropsychology

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## Introduction

Malnutrition is common in chronic alcoholics,

although its severity may depend on the social characteristics of the patient group under study and their severity of alcohol dependence<sup>1</sup>. Alcoholics represent the largest group of patients with treatable nutritional disorders in Western countries<sup>2</sup>.

Approximately 20-50% of individuals admitted to the hospital for alcohol withdrawal or Laennec's cirrhosis have been found to be hypocalcemic, and severe, symptomatic hypocalcemia is often seen in seriously ill alcoholics<sup>3</sup>. As many as 40% of decompensated cirrhotics may also manifest significant hyponatremia at the time of hospitalization<sup>4</sup>. Hypokalemia is also common in patients with alcoholic liver disease<sup>5</sup>. Hypokalemia is seen in approximately 50% of chronic alcoholics who are hospitalized for acute alcohol withdrawal and usually develops after their hospitalization. However, hypokalemia common in alcoholics does not always represent true potassium depletion. Although most cirrhotics have a diminished total body potassium content, intracellular potassium concentration is usually normal<sup>4</sup>. A number of studies have recorded low inorganic phosphorus concentrations in chronic alcoholics<sup>6, 7</sup>. On admission, 30% of patients with chronic alcoholism had hypophosphatemia<sup>8</sup>.

Alcoholism is the most commonly recognized cause of disturbed magnesium balance. Alcohol intake per drinking day correlated negatively with serum magnesium<sup>9</sup>.

Approximately 25-50% of the patients hospitalized for alcohol related problems are hypomagnesemic<sup>3</sup>. Low serum magnesium concentrations are frequently encountered especially during acute alcohol withdrawal<sup>10</sup>. Alcohol intake is also associated with low serum selenium levels. Among alcoholics admitted for detoxification, selenium was diminished despite the absence of severe malnutrition, as depressed blood selenium levels occur frequently in patients with chronic heavy ethanol ingestion even in the absence of severe liver disease or overt malnutrition<sup>11, 12</sup>. Among males, alcohol intake per drinking day correlated negatively with serum selenium. Among females, serum selenium con-

**TABLE 1.** Nutritional deficiencies in alcoholism.

Nutrients	Prevalence in alcoholism	References
calcium	20-50%	Pitts & van Thiel (1986) <sup>3</sup>
sodium	up to 40%	Pitts & van Thiel (1986) <sup>4</sup>
potassium	50%	Pitts & van Thiel (1986) <sup>4</sup>
phosphorus	30%	De Marchi et al. (1993) <sup>8</sup>
magnesium	25-50%	Pitts & van Thiel (1986) <sup>3</sup>
selenium	frequent	Dworkin et al. (1984) <sup>11</sup>
zinc		Valle et al. (1957) <sup>13</sup>
vitamins		
B <sub>1</sub> (thiamine)	30-80%	Morgan (1982) <sup>14</sup>
B <sub>2</sub> (riboflavin)	common	Rosenthal et al. (1973) <sup>15</sup>
B <sub>3</sub> (niacin)	35%	Leevy et al. (1965) <sup>16</sup>
B <sub>6</sub> (pyridoxine)	50%	Lumeng & Li (1974) <sup>17</sup>
B <sub>9</sub> (folate)	6-80%	Morgan (1982) <sup>14</sup>
vitamin C	14%	Roe (1979) <sup>18</sup>
vitamin D	58%	Bjorneboe et al. (1987) <sup>19</sup>
vitamin E	46%	Bjorneboe et al. (1988) <sup>20</sup>
vitamin K	58%	Iber et al. (1986) <sup>21</sup>

centration had a significant negative correlation with average daily alcohol intake, but not with alcohol intake per drinking day<sup>9</sup>.

Chronic alcoholism is also associated with low serum zinc level<sup>13</sup>. Low plasma, erythrocyte and hepatic zinc concentrations also follow chronic ingestion of alcohol<sup>22</sup>. Zinc values were also low in patients suffering from alcoholic cirrhosis<sup>23</sup>. The depression of zinc levels was related to the severity of the hepatic lesions, the lowest levels being observed among cirrhotics. Female alcoholics were more severely affected than males with respect to their zinc levels, although they consumed lesser amounts of alcohol and had a shorter duration of alcohol intake<sup>24</sup>. However, there is no indication for zinc supplementation in well-nourished alcoholics<sup>25</sup>, because the nutritional state of the alcoholics alone may not be an adequate explanation for their low serum zinc level<sup>26</sup>. A reduction in zinc concentration occurs in the central nervous system of chronic alcoholics<sup>27</sup>. It was shown that involuntary intoxication of rats with 10% ethanol solution for 8 months caused a reduction in zinc content in the brain<sup>28</sup>.

Thiamin deficiency, either overt or subclinical, has been reported in 30-80% of alcoholics<sup>14</sup>. Erythrocyte transketolase determination can be used to indicate a functional deficiency of thiamin<sup>18</sup>. Thirty-eight percent of alcoholics showed significant erythrocyte transketolase activation deficits indicative of severe thiamine deficiency<sup>29</sup>. Riboflavin deficiency is recognized as a common complication of chronic alcoholism<sup>15</sup>. Furthermore, pyridoxine deficiency, as measured by low plasma pyridoxal-5'-phosphate (PLP), was observed in more than 50% of alcoholics without abnormal hematologic indices of abnormal liver function<sup>17</sup>. Vitamin B<sub>12</sub> deficiency was rarely seen in chronic alcoholics<sup>30</sup>. Folic acid deficiency, either overt or subclinical, has been reported in 6-80% of alcoholics<sup>14</sup>. Folate deficiency is common in "derelict" chronic alcoholics with inadequate diet<sup>16, 30</sup>. Evidence of niacin deficiency is difficult to detect in alcoholics<sup>5</sup>. However, low circulating levels of nicotinic acid have been reported in 35% of chronic alcoholics<sup>16</sup>. Vitamin C is deficient in alcoholics with and without liver disease<sup>31</sup>. It was found that acute ethanol intoxication was accompanied by a decrease in the ascorbic acid content in the brain, liver and kidneys<sup>32</sup>.

Deficiencies of the fat-soluble vitamins A, D and E are not frequently reported in alcoholics without significant liver and/or pancreatic disease<sup>14</sup>. Alcoholics had significantly lower serum concentrations of vitamin A compared to a control group of healthy subjects. The depression of vitamin A levels was related to the severity of the hepatic lesions, the lowest levels being observed among cirrhotics. Female alcoholics were more severely affected than males with respect to their vitamin A levels, although they consumed lesser amounts of alcohol and had a shorter duration of alcohol intake<sup>24</sup>. Marrakchi et al<sup>33</sup>. suggest that attention should be paid to the vitamin A deficiency in erythrodermic or pustular psoriasis and to the vitamin E deficiency when these inflammatory diseases are associated with chronic alcoholism.

Alcoholics have low circulating levels of 25-hydrox-

vyitamin D<sup>5</sup>. Fifty-eight percent of the heavy alcohol consumers had a concentration of 25-hydroxyvitamin D<sub>3</sub> below lower limit of reference (20 ng/ml)<sup>19</sup>. Alcoholics were found to be deficient in vitamin E relative to controls<sup>34</sup>. Before abstinence, vitamin E levels were significantly depressed in alcoholics compared with the controls, in both plasma and erythrocytes<sup>35</sup>. Vitamin K deficiency is rare in alcoholics<sup>5</sup>. However, the production of abnormal prothrombin is frequently present in alcoholics and this may represent a subclinical vitamin K deficiency<sup>21</sup>.

Hypoglycemia occurs in patients drinking heavily and not eating<sup>36</sup>, but it seems that there is no significant caloric and protein undernutrition in alcoholic subjects<sup>37</sup>.

Circulating levels of vitamins can be a valuable guide to nutritional status, although care is needed when interpreting the results of such tests in alcoholics. Sensitive microbiological and biochemical tests for assessing vitamin status have been available for some years, and in addition, new biochemical methods are constantly being developed<sup>38</sup>.

### **Pathophysiology of nutritional deficiencies in alcoholism**

Chronic alcoholics are likely to develop multifactorial malnutrition. General causes of malnutrition in alcoholics are inadequate nutrient, particularly lack of water-soluble vitamins in their diet, reduced uptake and impaired utilization of nutrients<sup>18, 38</sup>. Alcohol not only depresses food intake by virtue of food displacement and suppressed appetite, but also by interfering with the absorption, storage, mobilization, activation, and metabolism of nutrients<sup>39</sup>. Hypomagnesemia and hypophosphatemia, which are very common in hospitalized alcoholics, result from deficient intake, malabsorption, excessive renal losses, and cellular uptake of both ions<sup>3</sup>. Alcohol causes urinary magnesium waste, but other mechanisms related to alcoholism contribute to the magnesium deficiency including malnutrition, gastrointestinal losses, phosphate deficiency, acidosis

and/or alkalosis, vitamin D deficiency and free fatty acidemia associated with alcohol withdrawal<sup>40</sup>.

Most dramatic is alcohol's effect on folate. When alcohol is present, it is as though the body were actively trying to expel folate from all its sites of action and storage. The liver, which normally contains enough folate to meet all needs, leaks folate into the blood. As blood folate concentrations rise, the kidneys are deceived into excreting folate, as though it were excess. The intestine normally releases and retrieves folate continuously, but it becomes damaged by folate deficiency and alcohol toxicity, as a result it fails to retrieve its own folate and misses out on any that may trickle in from food as well. Alcohol also interferes with the action of what little folate is left, and this inhibits the production of new cells, especially the rapidly dividing cells of the intestine and the blood. Alcohol abuse causes a folate deficiency that devastates the digestive function<sup>41</sup>.

Nutrient deficiencies are thus a virtually inevitable consequence of alcohol abuse, not only because alcohol displaces food but also because alcohol directly interferes with the body's use of nutrients, making them ineffective even if they are present<sup>41</sup>.

#### **a. Dietary intake**

Alcohol remains a prevailing cause of malnutrition resulting in a variety of deficient states secondary to decreased intake of nutrients<sup>42</sup>. General malnutrition is often reflected in body weight loss, mainly of adipose and muscle tissue. This loss of nutritional reserves is partly due to inadequate protein intake in the face of continued alcohol ingestion. Reduced dietary intake of vitamins and minerals in alcoholics contributes to specific nutrient deficiencies<sup>1</sup>.

Hypocalcemia in alcoholics can result from deficient intake<sup>3</sup>. Chronic alcoholism also results in thiamine deficiency as a result of inadequate dietary intake and of impaired absorption of the vitamin<sup>43, 44</sup>. Chronic alcohol feeding can induce riboflavin deficiency when intake of the vitamin is marginal<sup>44</sup>. Inadequate diet was often seen in alcoholics with reduced folate concentra-

tions<sup>30</sup>. Vitamin C levels, deficient in alcoholics with and without liver disease, correlate with dietary intake<sup>31</sup>. Plasma beta-carotene levels reduced to some extent among heavy alcohol drinkers below levels are due to differences in the carotene intake<sup>45</sup>. The causes of 25 (OH) D deficiency in alcoholics include inadequate dietary intake<sup>3</sup>. Intake of vitamin E was reduced by 62% among the alcoholics compared to the controls<sup>19</sup>. During periods of hard-drinking alcoholics had a markedly reduced intake of alpha-tocopherol compared to periods of moderate-drinking and abstinence<sup>20</sup>.

#### **b. Maldigestion and malabsorption**

In addition to various well-described primary malnutrition syndromes, secondary malnutrition may result from the interference of ethanol with nutrient digestion, absorption or utilization<sup>42</sup>. Alcohol inhibits absorption of vitamins and nutrients by active transport processes, an effect that may be crucial in precipitating specific nutrient deficiencies (e.g. thiamine) in alcoholics<sup>1</sup>.

Hypocalcemia in alcoholics can result from malabsorption<sup>3</sup>. Chronic alcohol abuse decreases the absorption of zinc<sup>46</sup>. Intestinal cells fail to absorb B vitamins, notably thiamine, folate, and vitamin B<sub>12</sub><sup>41</sup>. Impaired absorption occurs only in the presence of ethanol and is not observed after chronic administration or withdrawal<sup>47</sup>. Pyridoxine absorption is primarily passive and is affected only by very high concentrations of ethanol. Although all mechanisms (absorption, hepatic uptake or storage, urinary excretion) may contribute to folate deficiency, decreased absorption appears to be the most important quantitatively<sup>47</sup>. Chronic alcohol consumption impairs folate coenzymes, and causes possible malabsorption of enterohepatically circulated folates in folate deficiency even when other essential nutrients are provided<sup>48</sup>. Althausen et al<sup>49</sup>. reported that alcohol inhibited vitamin A absorption in humans. One of the causes of 25 (OH) D deficiency in alcoholics is malabsorption<sup>3</sup>.

#### **c. Impaired nutrient metabolism**

Alcohol abuse not only displaces nutrients from the

diet but also affects every tissue's metabolism of nutrients<sup>41</sup>. Low vitamin D activity may contribute significantly to calcium and phosphate deficiencies<sup>3</sup>. Ethanol (10%) ingestion enhanced the hepatic lipid peroxidation and decreased the calcium and magnesium contents in the blood and liver, thus chronic alcohol ingestion results in calcium and magnesium loss<sup>50</sup>. When alcohol is withdrawn, free fatty acids rise sharply and plasma magnesium falls<sup>51</sup>.

Alcohol has been reported to have a direct effect on zinc metabolism, and alcoholics are known to have reduced serum zinc levels<sup>13, 52</sup>. Abnormalities of zinc metabolism in chronic alcoholics are possibly secondary to homeostatic alterations associated with hepatic failure<sup>27</sup>. Alcohol-induced hepatitis may have caused a predisposition to altered zinc metabolism and possible zinc deficiency which was exacerbated by subsequent zinc deprivation<sup>53</sup>. Low plasma zinc concentrations may also be due to increased hepatic production of interleukin by Kupffer cells stimulated by ethanol or its metabolites<sup>54</sup>.

Alcohol may interfere with the conversion of thiamine to its active form, the coenzyme thiamine pyrophosphate, or impair utilization of the active form<sup>14</sup>. There is evidence to suggest that alcohol reduces thiamine phosphorylation to thiamine pyrophosphate (TPP) in the brain<sup>43</sup>. Impairment of thiamin metabolism in patients with alcohol dependence syndrome is possibly due to altered protein binding<sup>55</sup>. Similarly, ethanol interferes with the conversion of pyridoxine to its active form, the coenzyme PLP<sup>56</sup>. PLP is destroyed more rapidly in erythrocytes in the presence of acetaldehyde, the first product of ethanol oxidation, perhaps by displacement of PLP from its protective binding protein and its exposure to phosphatase<sup>17, 41, 57</sup>.

A common complication of chronic alcohol abuse is folic acid deficiency which can result from a direct effect of ethanol on folate metabolism, such as the acute decrease in serum folate levels<sup>58</sup>. *In vivo* hydrolysis of polyglutamyl folate was reduced by 35% in one

ethanol-fed minipig. Decreased hydrolysis of polyglutamyl folate may represent an early step in the development of folate deficiency in chronic alcoholics<sup>59</sup>. Ethanol also interferes with the formation and release of 5-methyltetrahydrofolic acid, the principal circulating form of folate, which is also the folate coenzyme necessary for DNA synthesis<sup>60, 61</sup>.

Enhancement of hepatic vitamin A degradation due to alcohol consumption is a likely explanation for vitamin A depletion<sup>14</sup>. Vitamin A deficiency may be secondary to zinc deficiency in alcoholics<sup>18</sup>. Low levels of vitamin A in cirrhotics may have arisen as a result of impaired mobilization from the liver due to zinc deficiency, or to non-availability of hepatic zinc. The depression of zinc and vitamin A levels was related to the severity of the hepatic lesions, the lowest levels being observed among cirrhotics<sup>24</sup>.

The causes of 25(OH)D deficiency in alcoholics include reduced hepatic 25-hydroxylase activity and lack of exposure to the sun.

Those with Laennec's cirrhosis also have low levels of vitamin D binding protein due to impaired hepatic protein synthesis and as a result, have low serum concentrations of total, but not free, 1,25-dihydroxyvitamin D<sup>3</sup>. New clinical evidence from heavy drinkers and from experimental work in rats suggests that alcohol may increase oxidation of alpha-tocopherol, causing reduced tissue concentrations of alpha-tocopherol<sup>62, 63</sup>.

#### **d. Decreased hepatic storage of nutrients**

Alcoholics with fatty infiltration of the liver have reduced hepatic concentrations of folate, riboflavin, nicotinamide, pantothenic acid, pyridoxine, vitamin B<sub>12</sub>, thiamine and vitamin A<sup>14, 64</sup>. Hepatic uptake of folate appears to be decreased by acute ethanol administration and hepatic accumulation of PLP is decreased significantly by ethanol<sup>47</sup>. Hepatic storage of vitamin A is reduced by ethanol<sup>65</sup>. Ethanol administration in animals was found to depress hepatic levels of vitamin A, even when administered diets containing large amounts of the vitamin, reflecting, in part, accelerated microsomal degradation through newly discovered microsomal

pathways of retinol metabolism, inducible by either ethanol or drug administration<sup>66</sup>.

#### **e. Increased nutrient requirements**

Alcoholics have increased nutrient requirements due to greater metabolic demands and the need for tissue repair<sup>38</sup>. Vitamins particularly required for tissue repair are folic acid, pyridoxine and vitamin B<sub>12</sub><sup>14</sup>.

#### **f. Increased urinary and fecal losses**

Increase in urination is associated with alcohol consumption<sup>41</sup>. The acute effect of ethyl alcohol ingestion is to induce diuresis with excretion of free water and the preservation of electrolytes. Excess water and electrolytes are acutely excreted in response to additional alcohol ingestion. With the cessation of alcohol intake, this excess will be excreted over several days<sup>67</sup>. The water takes with it important minerals such as magnesium, potassium, calcium, and zinc, depleting the body's reserves<sup>41</sup>.

Hyponatremia, common in decompensated cirrhotics, is caused by an impairment of renal free water clearance and concomitant water ingestion. Excessive proximal renal tubular sodium reabsorption and nonosmotic vasopressin release underlie the defect in renal water excretion in cirrhosis. In some alcoholics gastrointestinal and renal potassium losses and nutritional potassium deficiency may cause potassium depletion<sup>4</sup>. Hypocalcemia in alcoholics can result from renal calcium waste<sup>3</sup>. Induction of magnesium excretion by alcohol ingestion (167-260% of control values) occurs in chronic alcoholics<sup>51</sup>.

Overconsumption of alcohol may lead to severe zinc deficiency, probably via hyperzincuria<sup>52, 68, 69</sup>, because the decreased serum albumin levels may limit the availability of albumin for the transport of zinc in the plasma<sup>24</sup>. An increased loss of iron, aluminum and zinc through the intestine and kidneys, causing the preconditions for the development of deficiency of these metals in the body, was observed in males and females, engaged in sports, after a single intake of moderate doses of alcohol<sup>70</sup>.

Urinary loss of pyridoxine is accelerated by ethanol

and results in very low levels of both pyridoxine and PLP in plasma of alcoholics, particularly those with liver disease<sup>47</sup>. Acute ethanol administration in rats produces a marked increase in the urinary excretion of folate compounds, which leads to a decrease in plasma folate levels. The concentration of folate in the rat urine, as well as the amount of urinary folate excretion were markedly increased 4 hours after ethanol administration. After 14 hours, total plasma folate levels were significantly depressed to 50% of control levels<sup>71</sup>. Excess urinary folate excretion accumulated so that the longer the rats were exposed to ethanol, the greater the urinary loss<sup>58</sup>. Faizallah et al<sup>72</sup>. reported that alcohol produced a 47% increase in urinary ascorbic acid excretion in normal male volunteers. A similar ascorbiuresis in chronic alcoholics would be an additional factor in the causation of vitamin C deficiency in these patients.

#### **g. Genetics**

Another cause of the development of alcoholism may be a genetic predisposition to thiamine deficiency<sup>73</sup>. Blass and Gibson<sup>74</sup> propose that an inborn abnormality of the enzyme transketolase may be necessary before thiamin deficiency can lead to Wernicke-Korsakoff syndrome. An inborn error (i.e., high Km of transketolase for thiamine pyrophosphate) predisposing to thiamine deficiency diseases similar to those reported in Wernicke-Korsakoff syndrome may occur in the general population. However, this variant seems to occur more frequently among familial chronic alcoholic men and their male offspring without any history of alcoholism. The inheritance pattern of this enzyme variant as revealed from an Amish pedigree study may be autosomal recessive<sup>75</sup>. Polymorphisms of any of the enzymes that require TPP as a cofactor may account for genetic heterogeneity in the susceptibility to thiamine deficiency<sup>76</sup>. The substantial lag in formation of active holoenzyme and the findings of interindividual variation and cell type variation in the lag period suggest mechanisms for the loss of transketolase activity during thiamine deficiency and may explain, at least in

part, the differential sensitivity to deficiency demonstrated by tissues and individuals<sup>77</sup>.

### **Neuropsychiatric syndromes related with nutritional deficiencies in alcoholism**

Alcohol abuse causes impairment of cognitive functions ranging from mild forms to end-stage dementia<sup>78</sup>. Chronic alcoholics also exhibit a number of neurological disorders which are related to nutritional deficiencies<sup>79</sup>. Of particular importance are vitamin deficiencies such as thiamine, nicotinic acid, pyridoxine and vitamin B12 that are essential for normal cerebral functioning<sup>14</sup>.

The clinical presentation of brain damaged alcoholics is heterogenous and includes minimal cognitive impairment, amnesia and dementia. Thiamine malnutrition, affecting the diencephalon, can account for all clinical forms. Therefore, most organic brain syndromes in alcoholics can be considered as variants of the Wernicke-Korsakoff syndrome and rigorous attention should be paid to the nutritional status of all alcoholics<sup>80</sup>. Alcohol amnesic disorder seems to result from the combination of drinking, malnutrition, and genetic vulnerability to thiamine deficiency. Dementia associated with alcoholism is most likely a combination of intermediate brain syndrome and alcohol amnesic disorder<sup>81</sup>. Victor et al<sup>82</sup>. describes an over attack of Wernicke's encephalopathy as a prelude to the amnesic syndrome in well over 80% of cases. Clinical experience suggests that many cases of Korsakoff's psychosis develop their amnesic difficulties without any identifiable history of a Wernicke episode<sup>83</sup>. Thiamine deficiency seems to play a contributory (but not exclusive) role in the pathogenesis of alcoholic peripheral neuropathy. Deficiencies of other vitamins as well as direct neurotoxic effects of alcohol could also be involved in this phenomenon<sup>29</sup>.

Marchiafava-Bignami disease, resulting from vitamin B deficiency, is a special form of alcoholic thiamin deficiency, only to be distinguished from the Wernicke-Korsakoff syndrome by the peculiar distribution of

cerebral lesions (i.e., symmetrical degeneration of the central portion of the corpus callosum)<sup>18</sup>. Neurological pellagra was associated with Marchiafava-Bignami disease and/or Wernicke-Korsakoff disease in 13 of 22 cases of heavy alcohol drinkers. The possibility of pellagra occurring during thiamine and pyridoxine therapy and 'nicotinic acid deficiency' should be considered in alcoholic encephalopathies<sup>84</sup>. Ten of twenty folate deficient patients presented with a peripheral neuropathy, eight with subacute combined degeneration of the cord and two with myelopathy<sup>85</sup>. Folate deficiency may also contribute to the development of alcoholic polyneuropathy<sup>86</sup>.

### **Neuropathology of nutritional deficiencies in alcoholism**

The end result of malnutrition may be severe functional impairment and tissue damage in organs, mainly the liver and the brain, as a consequence of specific vitamin and nutrient deficiencies arising in chronic alcoholics<sup>1</sup>.

#### **a. Neuronal damage**

Central nervous system damage is a major complication of alcohol abuse<sup>87</sup>. Chronic alcohol-related brain damage can often be a direct result of nutrient depletion, particularly of the vitamins thiamine, B<sub>12</sub>, nicotinamide, and pyridoxine<sup>38</sup>. Disturbances in serum potassium levels (hypokalemia) as well as rapid correction of hyponatraemia may be associated with pontine swelling and dysfunction which, if undetected, leads to central pontine myelinolysis<sup>88</sup>.

Vitamin deficiency, particularly thiamine deficiency, plays a role in producing pathological and psychological changes of alcoholic brain damage<sup>87</sup>. Rats maintained on a thiamine-deficient diet for 38 days lost weight and displayed neurological symptoms. The PA value, representing the permeability of the blood-brain barrier to 14C-sucrose, significantly increased. Axonal degeneration was present in the olfactory glomeruli<sup>89</sup>. The loss of noradrenergic locus coeruleus neurons has been identified as the possible critical lesion inducing

amnesia in alcoholic patients with Wernicke-Korsakoff syndrome. However, thiamine deficiency does not result in a reduction in the number of pigmented cells in the locus coeruleus, and refutes the hypothesis that locus coeruleus cell loss is critical for amnesia in Wernicke-Korsakoff syndrome<sup>90</sup>. A significant loss of Nissl-stained neurons and a loss of parvalbumin-immunoreactive GABA-containing neurons was seen in the cerebral cortex of rats following alcohol treatment and thiamin deficiency. The results imply that thiamin deficiency is integrally involved in the pathogenesis of alcohol-related cortical neuronal loss<sup>91</sup>. In addition to their well-established diencephalic lesions, many Korsakoff patients have sustained widespread cerebral damage. Shrinkage in the frontal brain regions appear to be especially pronounced<sup>92</sup>. Axon terminal degeneration was seen in the olfactory bulbs and deep cerebellar nuclei in mice given the combined treatment of alcohol and thiamine deficiency<sup>93</sup>.

In some patients with alcoholic encephalopathies, chromatolysis similar to that reported in endemic pellagra was discovered on postmortem examination. The changes consisted of central chromatolysis, seen predominantly in the brainstem, especially in the pontine nuclei, where they were constant, and in the cerebellar dentate nuclei. Nuclei of cranial nerves (mainly the third, sixth, seventh and eighth), the reticular nuclei, arcuate nuclei and posterior horn cells, were also markedly affected. Changes were sometimes seen in the cerebral cortex, the interpeduncular nuclei, the central mesencephalic grey matter, the colliculi, the tenth and twelfth cranial nerves and perihypoglossal nuclei, the gracile and cuneate nuclei and anterior horn cells. This distribution was different from that reported in endemic and endogenous pellagra or in isoniazid-induced pellagra encephalopathy. The chromatolysis of alcoholic pellagra did not appear to be a retrograde change related to axonal degeneration. Microscopic examination of the pons is essential in alcoholic encephalopathies<sup>94</sup>.

#### **b. Vascular damage**

In Wernicke-Korsakoff syndrome, most prominent reductions of local cerebral blood flow were also seen in the hypothalamus and basal forebrain nuclei, but the thalamus, basal ganglia, and limbic systems were severely reduced. Chronic alcohol abuse, in the absence of thiamine deficiency, reduces cerebral blood flow by direct neurotoxic effects. If thiamine deficiency is also present, more severe and localized hemodynamic reductions are superimposed<sup>95</sup>.

#### **c. Neuroimaging studies**

Distinguishing ethanol neurotoxicity from nutritional deficiency can be facilitated by magnetic resonance imaging, which can visualize some of the specific macroscopic lesions of Wernicke's encephalopathy, central pontine myelinolysis, cerebellar degeneration, and Marchiafava-Bignami syndrome. Computerized morphometric studies of alcoholic brains have revealed ventricular enlargement, selective loss of subcortical white matter, and alterations in neuronal size, number, architecture, and synaptic complexity. These lesions tend to be more severe when there is coexisting nutritional deficiency or liver disease, suggesting that ethanol neurotoxicity may not be the sole cause<sup>96</sup>. Neuro-imaging studies have confirmed autopsy findings of more widespread structural and metabolic abnormalities in Korsakoff patients, particularly involving the frontal lobes<sup>97</sup>. However, CT findings on thiamine-deficient patients did not differ from those on patients without thiamine deficiency, and correlations between thiamine deficiency and subcortical atrophy before treatment were not significant. It is believed that there is a reversible brain shrinkage in chronic alcoholics<sup>98</sup>.

#### **Neurophysiology of nutritional deficiencies in alcoholism**

Brain dysfunction sustained with cumulative subclinical episodes of thiamin deficiency during periods of alcohol abuse may facilitate the development of tolerance and physical dependence that may cause progressive increases in alcohol consumption and further brain



damage<sup>76</sup>. Prolonged consumption of alcohol results in alterations of immune responses, ultimately manifested by increasing susceptibility to infectious agents. Such changes can be due to nutritional deficiency, as well as to the direct effects of alcohol or its metabolites on immune cells, oxidative stress, and neutrophil dysfunctions<sup>99</sup>.

#### **a. Neurotransmitter dysfunction**

Hyperexcitability following chronic alcohol exposure appears to result in enhanced activation of glutamatergic synapses in the brain. This enhanced glutamatergic transmission probably results from a combination of increased NMDA receptor activation, decreased GABA<sub>A</sub> receptor activation and increased function of voltage-activated calcium channels<sup>100</sup>. It has been hypothesized that low brain zinc, noted in chronic alcoholics, enhances N-methyl-D-aspartate (NMDA) excitotoxicity<sup>101</sup>. Studies suggest that NMDA receptor-initiated excitotoxicity may result from alcohol-related thiamine deficiency. Therefore, excitotoxic damage due to neural compensation for sustained alcohol levels and nutritional deficits may underlie aspects of alcohol-related brain damage<sup>100</sup>.

#### **b. Ion channel dysfunction**

Alcohol produces rapid brain intracellular acidosis due to the loss in brain [Mg<sup>++</sup>]. Binge or heavy drinking of alcohol may result in stroke-like events and sudden death via rapid alterations in brain cellular bioenergetics<sup>102</sup>.

#### **c. Oxidative stress**

The reduced plasma levels of alpha-tocopherol and selenium after heavy consumption of ethanol may be of particular interest in view of the protective effect exerted by antioxidants towards cell damage<sup>19</sup>. The reduced alpha-tocopherol and selenium may influence the maintenance of normal cell structure and functions, and contribute to development of diseases frequently observed in alcoholics<sup>20</sup>. Prior to abstinence, glutathione peroxidase activity and selenium and vitamin E levels were significantly depressed in the alcoholics.

There is a deficiency in the antioxidant defense system of chronic alcoholics before the occurrence of severe liver disease<sup>35</sup>. Also, zinc deficiency in alcoholics can produce neuronal damage through increased free radical formation<sup>101</sup>. The DNA excision-repair capacity of lymphocytes measured as unscheduled DNA synthesis induced by N-methyl-N-nitrosourea in lymphocytes was decreased in alcoholics, and lipid peroxidation in plasma was significantly higher as a consequence of alcohol overconsumption. A negative correlation was found between lipid peroxidation and vitamin C levels and between unscheduled DNA synthesis and lipid peroxidation values. These results support the hypothesis of a connection between cell membrane status and DNA damage and repair and the possible role of active oxygen species in cell damage caused by ethanol<sup>103</sup>.

#### **d. Metabolic dysfunction**

Zinc deficiency decreases alcohol dehydrogenase activity and thus slows down the elimination of ethanol<sup>104</sup>. A grossly disturbed pattern of amino acids in the blood of patients undergoing treatment for alcohol withdrawal syndromes is likely to be caused by loss of hepatic function and brain damage caused by B group vitamin deficiency<sup>44</sup>. Damage to the protein moiety of some of the thiamin-using enzymes has possible mechanisms of brain cell necrosis<sup>105</sup>. There is evidence to suggest that alcohol reduces thiamine phosphorylation to TPP in the brain. TPP is a cofactor for the pyruvate dehydrogenase complex, alpha-ketoglutarate dehydrogenase and transketolase, three enzymes involved in cerebral glucose and energy metabolism<sup>39</sup>. Decreased activity of the transketolase enzyme is an essential abnormality of Wernicke-Korsakoff syndrome<sup>18</sup>. Transketolase may serve a role as an intracellular thiamine "sink" that would provide for the unidirectional, active transport of thiamine across neuronal membranes. Transketolase could not only provide TPP to replace released thiamine, it also provide a means for the uptake of thiamine in conjunction with released neurotransmitters following neural firing. A transketolase with reduced affinity for TPP could lead

to impaired ion channel and/or excitatory amino acid inactivation, especially during extreme thiamine deficiency and periods of neural hyperexcitability following chronic alcohol consumption<sup>76</sup>.

Chronic ethanol ingestion also significantly reduces regional brain thiamine pyrophosphokinase activity<sup>106</sup>, which is essential for the phosphorylation and intracellular accumulation of thiamine. In this way, the availability of TPP can be decreased, contributing to the depression of the tricarboxylic acid cycle, in which TPP plays an important role. In other words, the depression of thiamine cerebral metabolism may be both a cause and an effect of the depressed energy metabolism which is observed in chronic alcoholism. It is noteworthy that chronic ethanol intake depresses cerebral thiamine metabolism when dietary thiamine intake is adequate or even abundant<sup>107</sup>.

Folates are a group of compounds which are required in the diet and are important in DNA, amino acids and possibly also amine metabolism<sup>108</sup>. The folic acid and vitamin B<sub>12</sub> metabolism are intimately related. Folate and vitamin B<sub>12</sub> are required for the synthesis of purines and pyrimidines, and therefore, are important for nucleic acid and nucleoprotein synthesis<sup>109</sup>. A single biochemical reaction, the methionine synthetase reaction, is suggested as the basis for neurological as well as haematological consequences of both vitamin B<sub>12</sub> and folate deficiency<sup>85</sup>.

### **Neuropsychology of nutritional deficiencies in alcoholism**

Chronic alcoholic patients frequently exhibit a mild to moderate cognitive impairment, including impairment in perceptual-motor skills, visual-spatial functions, learning/memory, and abstraction and problem solving, that has been related to Wernicke-Korsakoff encephalopathy and attributed tentatively to nutritional and vitamin deficiencies<sup>81, 110</sup>. Alcoholics scored significantly lower in intellectual and visuospatial tasks, but not in verbal memory tasks<sup>110</sup>. Multiple correlations between measurements of the thiamin parameter trans-

ketolase activity and test performances were found in the alcoholic patients. Thiamin substitution decreased the percentage of weak test performances<sup>111</sup>. In Korsakoff patients, despite normal IQs, a wide range of cognitive deficits, including impairment in perceptual-motor skills, visual-spatial functions, learning/memory, and abstraction and problem solving are pronounced, especially in episodic memory and new learning. Procedural memory (learning of simple, repetitive skills), however, is relatively intact. New evidence suggests that orbitobasal frontal lobe dysfunction in addition to diencephalic lesions contributes to the deficits found in Korsakoff patients. Whereas structural and/or neurochemical abnormalities within the limbic/diencephalic circuits account for anterograde amnesia, some other factor, such as frontal lobe dysfunction, must underlie the severe retrograde memory loss which is characteristically found in Korsakoff's syndrome<sup>97</sup>. Prognosis for the recovery from Korsakoff's syndrome is poor, although evidence suggests that these patients should be able to learn simple repetitive tasks involving procedural memory<sup>112</sup>.

The development of suitable computerized psychometric tests may allow earlier detection of brain malfunction associated with malnutrition, which can be reversed by nutrient repletion before permanent damage occurs<sup>38</sup>.

### **Conclusion**

There are a number of nutritional deficiencies which need to be cared for, but magnesium, thiamine, and other B vitamins need to be administered immediately. Potassium and phosphorus should be supplied when they are low<sup>51</sup>. Restriction of water intake is the principal therapeutic measure for hyponatremia<sup>4</sup>. Magnesium replacement therapy is recommended to prevent some of the serious sequelae of magnesium deficiency<sup>40</sup>. Hypocalcemia in chronic alcoholism is responsive only to magnesium therapy<sup>51</sup>. Short-term oral magnesium therapy may improve liver cell function, electrolyte status, and muscle strength in chronic alcoholics<sup>113</sup>. In

addition, magnesium ions can act as local vasodilators on brain microvessels and possess antispasmodic activities on brain arterioles and venules. Magnesium may be useful in the treatment and prevention of alcohol-induced brain vascular damage<sup>114</sup>. For people made sick by excessive alcohol intake and requiring detoxification, repletion therapy has to be instituted early in order to bring magnesium and potassium levels back to normal as quickly as possible<sup>41</sup>. Clinically, zinc replacement therapy may be a rational approach to the treatment of alcohol withdrawal seizures and alcohol-related brain dysfunction<sup>101</sup>.

Supplement of thiamine is essential for alcoholics, even in currently abusing patients<sup>5,55</sup>. For clinical practice, thiamin substitution seems to be highly indicated during stationary withdrawal treatments, because there is no amelioration of the thiamin status with hospital diet and alcohol withdrawal alone<sup>111</sup>. If doubt exists as to the presence of Wernicke's encephalopathy, then parenteral thiamine should be administered<sup>115</sup>.

Fortification of alcoholic beverages with thiamine may prevent or reduce thiamine deficiency in alcoholics<sup>116</sup>. It appeared to aggravate the neurological state or to trigger the development of alcoholic pellagra encephalopathy in some patients having received thiamine and pyridoxine therapy without niacin. Multiple vitamin therapy should be administered in the treatment of undiagnosed encephalopathies in alcoholic patients<sup>84</sup>. The appearance of macrocytic anemia is a late deficiency sign, and therefore, in situations of an increased need and in patients included in the risk groups, a supplemental intake must be given in order to avoid irreversible lesions if it is not possible to monitor folate levels. There are risk groups (old people, patients with liver disease, alcoholics) in which various etiological factors come into play, acting at a different metabolic levels on folates and making their dietetic or pharmacological compensation more difficult even if supply is considerably increased<sup>117</sup>.

Optimal health is a result of dietary optimization. Attainment of optimal health rather than prevention of

deficiency symptoms is the goal. There can be little doubt that in this respect the requirements for vitamin C are greater than the amount required for the mere prevention of overt or classical scurvy. The lowest level is that value which prevents deficiency symptoms. The second level is valid for healthy populations (< 200 mg/d). This level would take into account needs which differ based on age, sex, physical activity, physiological status (e.g. pregnancy or lactation) and environmental factors such as smoking, pollution and alcohol intake<sup>118</sup>.

Alcoholics should be screened periodically for vitamin D deficiency and osteopenia, and when either is detected they should receive vitamin D supplements<sup>3</sup>. Patients who received nutrition therapy reported significantly less alcohol cravings as well as significantly greater nutrient intakes, and a greater number abstained from alcohol. These findings indicate that nutrition therapy can aid in the recovery from alcoholism<sup>119</sup>.

Although abstinence and proper nutrition remain the cornerstones of treatment, pharmacological modification of neurotransmitter function and/or enhancement of cerebral metabolism combined with behavioral methods may also be beneficial. Serotonergic approaches to improve memory in detoxified alcoholics may also reduce alcohol intake, and this has implications for treatment of less impaired alcoholics<sup>120</sup>. Lithium nicotinate showed the greatest activity in suppressing ethanol dependence in rats induced by a three-month administration of alcohol. The efficacy of the drugs correlated with the normalization of the activity of alcohol dehydrogenase, catalase and the levels of nicotinamide coenzymes and lipid peroxides in the brain, liver and kidney<sup>121</sup>.

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