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Alcohol Drinking Patterns and Nutrition in Alcoholic Liver Disease

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1. Introduction

In most Western countries alcoholic beverages contribute markedly to the overall caloric intake. Indeed, alcohol contributes to approximately 5% of the daily caloric intake in the American diet (Halsted, 2004). Alcohol, besides nicotine, is also the most widely used drug in our society, bearing a large potential for addiction but also organ damage and herein particularly liver damage. Chronic alcohol abuse is frequently accompanied with malnutrition with the degree of malnutrition varying not only between the type of alcohol abuse (e.g. binge drinker vs. chronic drinker) but also the degree of liver damage. For practitioners it is important to recognize the various factors contributing to the evolvement of malnutrition in alcoholic patients, as the correction of deficiencies or other strategies to improve nutritional status may have a beneficial effect in the prevention and treatment of alcoholic liver disease. The effects of alcohol ingestion on dietary pattern, nutrient intake and the intermediary metabolism have been investigated in numerous human but also animal studies. In this chapter the role of alcohol as energy source but also the effects of alcohol ingestion on energy metabolism, dietary pattern and micronutrient bioavailability as well as metabolism with special emphasize on the liver and the development of alcoholic liver disease are reviewed. Furthermore, current recommendations for treatment of malnutrition in patients with alcoholic liver disease are summarized.

2. Alcohol drinking patterns

When talking about "alcohol drinking", two main patterns have to be distinguished: acute "binge drinking" and "chronic drinking". As reviewed by Zakhari and Li (2007), the impact of the quantity and frequency of alcohol ingestion on alcoholic liver disease becomes more and more important. Indeed, the results of a Danish prospective study with a cohort of 6152 alcohol misusing men and women indicate that periodic drinking leads to a significantly lower relative risk for developing cirrhosis than daily drinking (Kamper-Jorgensen *et al.* 2004). The Italian Dionysos Study focused on drinking habits as cofactors of risk for alcohol-induced liver damage. The results of this study show that drinking without food and drinking multiple different alcoholic beverages both increase the risk of developing alcoholic liver disease (Bellentani *et al.* 1997). Furthermore, it has been shown that the metabolic effects of binge drinking and chronic drinking on the liver also markedly differ (for overview see (Zakhari and Li, 2007)). For example, binge drinking may lead to glycogen

depletion, acidosis and hypoglycemia; whereas chronic drinking results in the development of alcoholic liver damages. The differences between these two alcohol drinking patterns are detailed in the following.

2.1 Binge drinking

The World Health Organization (WHO) defines binge drinking as a pattern of heavy drinking that occurs in an extended period, which is usually defined as more than one day of drinking at a time (WHO, 1994). In the United States (US), the National Institute on Alcohol Abuse and Alcoholism defined a more common definition that a "binge" is a pattern of alcohol drinking that brings blood alcohol level to 0.08 gram-percent or above. For a typical adult, the amount of alcohol that has to be ingested to reach these blood alcohol levels is on average equivalent to consuming five or more drinks (men), or four or more drinks (women), in about two hours (National Institute on Alcohol Abuse and Alcoholism, 2007). In contrast, in the United Kingdom binge drinking is defined as the consumption of more than eight drinks in men and more than six drinks in women in a single day (Institute of Alcohol Studies, 2010). In the United States, the prevalence of binge drinking among adults was 15.2% in 2009, with the prevalence being two times higher in men than in women (Kanny *et al.* 2011). This phenomenon can also be observed in most of the European countries, except for England and Ireland. In these two countries binge drinking is found to be particularly prevalent in women (Dantzer *et al.* 2006). In terms of age, the prevalence of binge drinking decreases, both in the United States and United Kingdom, with increasing age, indicating that the phenomenon "binge drinking" is as an important problem especially in young people (Institute of Alcohol Studies, 2010). In dependence on "drinking cultures" binge drinking occurs more or less in different countries. In Mediterranean culture, alcoholic beverages, especially wine, are consumed on a daily basis as part of meals and mostly in family settings. In contrast, in Northern cultures, drinking is less frequent in everyday life but heavier, typically around weekends (Institute of Alcohol Studies, 2010).

2.2 Chronic drinking

In a systemic review, the risks of moderate alcohol consumption have been weighed against its benefits. As a result of comparing the critical endpoints of alcohol intake related to morbidity and mortality, tolerable upper alcohol intake levels have been defined for the German adult population to be 20 to 24g alcohol per day for men and 10 to 12g alcohol per day for women (Burger *et al.* 2004). However, it is recommended that if this amount of alcohol is ingested, at least two days per week should be without any alcohol consumption. Exceeding this tolerable alcohol intake level alcohol consumption is classified as a risk factor for numerous organ damages (e.g. liver, pancreas, stomach, gut).

In Germany, the per-capita consumption of pure ethanol was 9.7 l in 2009. Furthermore, in 2006 3.8% of the German population met the criteria of alcohol abuse and 2.4% of alcohol dependence in 2006 (Deutsche Hauptstelle für Suchtfragen, DHS, 2006). According to the 2001-2002 National Epidemiologic Survey on Alcohol and related Conditions, 5.8% of the US adult population meet the criteria for alcohol dependence or alcoholism and 7.1% meet the criteria for alcohol abuse (for overview see Zakhari and Li, 2007). Despite intense education on the risks associated with alcohol abuse, in industrialized countries in Europe as well as in the United States, the damage of liver and other organs as a consequence of

chronic alcohol consumption is still an important health problem. Especially, chronic alcohol abuse is one of the most important risk factors for liver damage (Lieber, 1994). The results of previous studies demonstrated the existence of a dose-response relation between alcohol intake and the risk of liver disease (Lelbach, 1975; Day, 1997). As a consequence of alcohol abuse different alcoholic liver disease patterns such as alcohol-caused fatty liver, alcoholic hepatitis, or alcohol-induced cirrhosis can be observed.

3. Alcohol and energy metabolism

3.1 Alcohol and its contribution to energy intake

For many people regular alcohol consumption is still a part of their daily diet. Raw alcohol and even more so alcoholic beverages are rather energy dense nutrients. Alcoholic beverages primarily consist of water, ethanol, and, depending on the beverage, variable amounts of carbohydrates as well as to a lesser extend proteins, vitamins or minerals (see Table 1).

	Energy	Protein		Fat		Carbohydrate		Ethanol	
	kcal	g	kcal	g	kcal	g	kcal	g	kcal
Whiskey	250	0.0	0.0	0.0	0.0	0.1	0.4	36	252.0
Vodka	232	0.0	0.0	0.0	0.0	0.0	0.0	33.4	233.8
Dry red wine	60	0.7	2.9	0.0	0.0	4.6	18.9	5.5	38.5
Dry white wine	42	0.5	2.1	0.0	0.0	3.1	12.7	4.0	28.0
Stout	83	0.1	0.4	0.0	0.0	3.8	15.6	19.9	139.3
Beer	67	0.1	0.4	0.0	0.0	0.2	0.8	9.5	66.5
Sweet white wine	96	0.2	0.8	0.0	0.0	5.9	24.2	10.2	71.4
Cocktail	141	0.2	0.8	0.9	8.4	9.1	37.3	13.7	95.9

Table 1. Energy and caloric content of various alcoholic beverages per 100 mL. Values were calculated with the software program EBIS pro and are based on the German food index.

Calories provided through the consumption of alcoholic beverages primarily stem from its content and metabolism of carbohydrates and ethanol. Indeed, hard spirits like whiskey, vodka and schnapps contain no sugar, whereas dry red and white wine contain 31 to 46 grams of sugar per liter. Sugar content of beer various between 2 and 38 grams per liter depending whether stout or "normal" beer is consumed. Sugar content may even be as high as 120 grams per liter in sweet white wine (on average 59 g/L) and up to 91 grams per liter in mixed cocktails (average value of several cocktails). A similarly strong variability in content is also found when ethanol contents of different alcoholic beverages are compared. For example, a liter of beer with the exception of stout on average contains 200 grams of ethanol per liter whereas wine contains 40 to 100 grams of ethanol per liter. Hard spirits may even contain up to 300 to even 500 grams of ethanol per liter. An average serving of wine (125 mL), beer (330 mL) or hard spirits (40 mL) contains 12 to 14 grams of ethanol.

3.2 Alcohol metabolism and energy yield

Using bomb calorimetry it was shown that ethanol yields 7.1 kcal (= 29.3 kJ) per gram when completely combusted (Lieber, 1991). However, as the digestibility of ethanol ranges from 98 to 100 % and approximately 5% of ethanol is also lost through respiration, faeces and urine energy provide for metabolic purposes is only approximately 6.9 kcal per gram ethanol (= 28.8 kJ per gram ethanol) (Lieber, 1991). It was further shown that even when ethanol is ingested at constant rates and high levels (e.g. up to 171 grams of ethanol per day) the loss of alcohol derived energy through the respiratory tract und urine only accounts to approximately 50 kcal per day (Reinus *et al.* 1989). Indeed, a marked loss of ethanol through urine or respiration was only observed when the amounts of ethanol ingested exceed the liver´s ethanol metabolizing capacity shown to be 105 mg/ kg body weight per h (Reinus *et al.* 1989).

Taking the caloric content of alcoholic beverages into account and the fact that only little is lost through respiration, faeces, and urine, one would expect a positive association of alcohol intake and obesity. However, results of epidemiological studies are somewhat contradictory indicating no or only a weak association of alcohol consumption and body weight in men and even an inverse association in women (Müller *et al.* 1999). The results of these studies suggest that

- ethanol either bears a negative effect on energy yield implying that ethanol is inefficiently metabolised or
- the consumption of ethanol alters dietary intake, absorption and/ or metabolism of other nutrients subsequently leading to a negative or at least diminished energy yield.

In the very early studies of Atwater and Benedict (1902), using direct calorimetry it was shown that in healthy non-alcoholic volunteers ethanol (72 grams ethanol per day) was utilized as efficiently as fat or carbohydrates as a source of energy. Furthermore, it was shown that the ingestion of 31.5 gram of ethanol per 65 kg of body weight did not increase oxygen consumption or thermogenesis in normal volunteers (Barnes *et al.* 1965). However, contrary to these early finding, in the studies of Pirola and Lieber (1972), in which it was shown in normal volunteers that the progressive substitution of carbohydrates with ethanol in an otherwise balanced, normal diet results in a decrease in body weight. In line with these findings it was further shown that the addition of 90g of ethanol to the daily diet increased the daily energy expenditure by 7% (Suter *et al.* 1992) and that lipid oxidation may be inhibited by the ingestion of additional alcohol to 50% of calories (Sonko *et al.* 1994). Furthermore, in a study in which the energy intake of middle-class patients with alcoholic liver disease ranging from non-cirrhotic to cirrhotic was compared to that of controls with the same body mass index it was shown that non-alcoholic energy intake did not differ from that of controls (Bergheim *et al.* 2003). In this study it was further shown that the average energy intake form alcoholic beverages (e.g. from beer, wine and hard spirits) accounting to ~1008 kcal/ day (= ~142 g Ethanol/ day) was added to the daily non-alcoholic energy intake without leading to the development of obesity. The results of this study are in line with other studies in which it was also shown that in middle-class alcohol consumers alcohol consumption is not associated with increased body weight compared with control subjects ingesting the same nonalcoholic energy intake, but lower total energy intake (Mezey, 1991; Rissanen *et al.* 1987). These data suggest that some of the energy ingested as alcohol is "lost" or "wasted"- that is, this energy is not available to the body for the production of energy

resources that can be used to produce or maintain body mass. However, when interpreting these data, it has to be kept in mind that when assessing nutritional intake and herein especially that of alcohol underreporting may be a problem. For example, when applying the formula published by the WHO to calculate for underreporting to a study performed by Colditz *et al.* (1991) underreporting was found in ~25% of women and ~33% of men (Müller, 1999).

Several mechanisms have been proposed to be responsible for the apparent loss of alcohol-derived energy. In the following, some of the main mechanisms proposed are summarized.

Three enzyme systems are known to be able to metabolize ethanol to acetaldehyde:

- the alcohol dehydrogenase (ADH), a cytolic enzyme existing as several isoenzymes, is the major enzyme metabolizing ethanol
- the microsomal ethanol oxidizing system (MEOS), a cytochrome P450-depending enzyme system, bound to the smooth endoplasmatic reticulum
- the catalase, localized in the peroxisomes, under normal conditions plays a neglectable role and therefore shall not be discussed here (for overview also see Zakhari (2006)).

The ADH is the major enzyme metabolizing ethanol. In order to facilitate the oxidation of ethanol ADH converts its cofactor nicotinamide adenine dinucleotide (NAD^+) to NADH. The reaction mediated by the ADH are summarized as

$$\text{Ethanol} + NAD^+ \rightarrow \text{Acetaldehyde} + NADH$$

NADH is an energy rich molecule that can donate electrons to the electron transport chain in the mitochondria subsequently leading to the synthesis of adenosine triphosphate (ATP). However, as the ADH-mediated ethanol oxidation is located in the cytoplasm and NADH cannot pass the mitochondrial membrane the cellular redox potential is markedly altered when ethanol is metabolised (e.g. the NADH/ NAD^+ ratio) (van Haaren *et al.* 1999). As a consequence, ethanol derived NADH is mainly metabolized through the reduction of pyruvate to lactate and oxaloacetate to malate which in turn can then be used to utilize energy by the mitochondria (van Haaren *et al.* 1999). Acetaldehyde also produced in this reaction is rapidly metabolized, mainly by mitochondrial acetaldehyde dehydrogenase (ALDH) 2 to form acetate and NADH, which than is oxidized by the electron transport chain (for overview also see (Zakhari and Li, 2007)). The increase in mitochondrial NADH in hepatocytes resulting from the metabolism of acetaldehyde may result in a saturation of the NADH dehydrogenase and subsequently the impairment of the tricarboxylic acid (TCA) cycle as the acetyl coenzyme A (CoA) synthase 2, the mitochondrial enzyme involved in the oxidation of acetate is not found in the liver but is abundant in heart and skeletal muscles (Fujino *et al.* 2001). As a consequence, most of the acetate resulting from the breakdown of ethanol in the liver enters the circulation and is eventually metabolized to CO_2 in the TCA in tissues that possess the enzymes to convert acetate to acetyl CoA (e.g. heart and skeletal muscle).

Furthermore, ethanol is also metabolised through the MEOS. The MEOS differs from the ADH in several aspects as it has a higher Michaelis constant (K_m) (MEOS: K_m 10mM vs. ADH: K_m 1mM) (Haseba and Ohno, 2010; Lieber and DeCarli, 1970) and its activity increases when ethanol is consumed chronically (Lieber, 1997). The reaction mediated by the MEOS, which requires Nicotinamide adenine dinucleotide phosphate (NADPH) rather than NAD^+ and oxygen as a cofactor are summarized as

$$\text{Ethanol} + \text{NADPH} + H^+ + \tfrac{1}{2} O_2 \rightarrow \text{Acetaldehyde} + NADP^+ + 2H_2O$$

This metabolic route of ethanol was proposed as one possible explanation of the energy "waste" associated with the intake of alcohol (Lieber, 1994; Lieber, 2003). Lieber (1991) postulated that when alcohol is consumed chronically alcohol is metabolized preferentially through the MEOS implying that the production of $NADP^+$ is increased whereas the formation of NADH through the ADH is decreased. This shift between the two enzyme systems would imply a loss in the net energy gain (e.g. through MEOS "only" ~67% of the energy gain that is achieved if ethanol is metabolised through ADH). Lands and Zakhari (1991) calculated that if ethanol is readily metabolized through mitochondrial oxidation 1 Mol of ethanol can provide as much as 16 Mol of ATP. In contrast the first steps of microsomal-mediated ethanol oxidation require 1 Mol of NADPH equivalent to 3 Mol ATP. Subsequently the energy yield through this pathway is markedly lower.

In addition, it was also postulated that the metabolism of acetate may also be associated with a loss of energy. Indeed, Müller *et al*. (1995 and 1998) showed that up to 80% of the acetate derived from ethanol metabolism in the human liver was found in the liver vein. It was further shown that in fasted subjects acetate blood levels raise with 90 min after ethanol ingestion up to 900-950 Mol/L after the ingestion of 47.5 g ethanol (Frayn *et al.* 1990). At the same time, acetate uptake by muscle tissue only accounted to ~3% of the ingested ethanol. The enhanced energy use needed for the lipogenesis of acetate actually was calculated to account to ~25% of the energy content of ethanol (Müller *et al*. 1999).

3.3 Alcohol metabolism and its effect on general energy as well as fat, protein and carbohydrate metabolism

The increased ratios of NADH to NAD^+ in both mitochondria and cytosol in hepatocytes affect the "direction" of several reversible reactions resulting in alterations of hepatic lipid, carbohydrate, and protein but also lactate and uric acid metabolism. The latter are not discussed in this chapter. Most of these changes have been shown to happen as a consequence of acute excessive alcohol intake (e.g. binge drinking) and seem to be at least in part to be attenuated when alcohol is consumed chronically; however, some alterations, like the accumulation of fat in the liver are also found when alcohol is consumed chronically. Furthermore, it has been shown that acute but also chronic intake of alcohol may not only affect micronutrient uptake in the small intestine but may also disturb the absorption of macronutrients; however, most of the data summarized in the following stem from animal experiments.

3.3.1 Effect of alcohol intake on fat metabolism

Besides an altered dietary pattern (e.g. higher intake of pork and subsequently polyunsaturated fatty acids) found to be associated with an increased intake of alcohol (French, 1992) results of early animal studies suggested that the concomitant ingestion of alcohol and plant derived oils is associated with a markedly reduced absorption of these fats (Bode, 1980); however, this effect of alcohol was probably due to a slowed gastric empting resulting from the combination of the oil with a relatively high dose of alcohol. In later human and animal studies it was found that absorption of lipids decreased by the ingestion of alcohol doses of ≥ 1g/ kg body weight (Bode and Bode, 1992). It has further been

suggested, that fat malabsorption found in patients with alcoholic hepatitis may be due to reduced bile and pancreas enzyme secretion (Soberon *et al.* 1987). Regarding the effects of alcohol metabolism on hepatic lipid metabolism it has been shown that the altered ratio of NADH/ NAD^+ results in an increase of the intermediate metabolite α-glycerophosphate, which favours the accumulation of triglycerides in hepatocytes, but also inhibits β-oxidation of fatty acids in mitochondria (for overview also see Zakhari and Li (2007); Lieber (1984)).

3.3.2 Effect of alcohol intake on protein metabolism

In Europe the average intake of proteins has been shown to be normal in patients with chronic alcohol abuse or alcoholic liver disease in the earlier stage (e.g. steatohepatitis) (Bergheim *et al.* 2003). However, results of animal but also human studies suggest that absorption of amino acids in the small intestine is markedly impaired when alcohol is consumed concomitantly. Indeed, it has been shown in animal studies that in the presence of 2-4.5% of alcohol the uptake of L-alanin, L-glycine, L-leucine, L-proline, L-methionine, L-phenylalanin, and L-valin is in the small intestine impaired by more than 20% (Abidi *et al.* 1992). Especially the decreased uptake of methionine but also the inhibition of the methionine synthase in combination with the deficiency of folic acid and pyridoxine has been shown to be a critical factor in the development and progression of alcoholic liver disease. Recent data from animal studies suggest that the shift in the NADH/ NAD^+ ratio resulting from alcohol metabolism may also affect liver methionine metabolism (Watson *et al.* 2011). Indeed, it has been shown that the supplementation of methionine but also its metabolite S-adenosyl-L-methinone may improve alcoholic liver disease (for overview also see Beier and McClain (2010)).

3.3.3 Effect of alcohol intake on hepatic glucose metabolism

In animal experiments it was shown that alcohol at concentrations found in humans after moderate drinking (e.g. 1-5% w/v) depresses glucose uptake in the brush border membrane in a dose- and time-dependent manner (Dinda and Beck, 1981). Furthermore, the increase in NADH resulting from the ADH-mediated oxidation of alcohol has been shown to prevent the conversion of pyruvate to glucose, which in turn impairs the rate limiting step of the gluconeogenesis, the pyruvate carboxylase reaction (Krebs *et al.* 1969) subsequently leading to hypoglycaemia. Fasting, sustained physical exercise and malnutrition may even increase the likelihood of hypoglycaemia.

4. Alcohol and dietary pattern

Alcohol consumption and potential alterations of dietary habits have been extensively studied in various cohort studies in various regions of the world (Thomson *et al.* 1988; Gruchow *et al.* 1985; Suter *et al.* 1997).

4.1 Binge drinking and dietary pattern

Kim *et al*. (2007) reported that both male and female binge drinkers have higher energy intake in comparison to non-binge drinkers. Among men, an inverse association between the frequency of binge drinking and the intake of polyunsaturated fatty acids (PUFA) including linoleic acid, α-linolenic acid and eicosapentaenoic acid was found; a similar

association was not found in female binge drinkers (Kim *et al.* 2007). The lower intake of PUFA implies that binge drinking affects the choice of foods (e.g. intake of fish maybe lower) (Howe *et al.* 2006). Results of Toniolo *et al.* (1997) indicate that moderate drinkers (< 5 g/d) have reduced intake of milk and fresh fruits in comparison to abstainers (Toniolo *et al.* 1991). However, results of Thomson *et al.* (1988) found higher intake of fiber, cereal fiber and PUFA in moderate drinking group (0.1-9 g/day). Results of Colditz *et al.* (1991) found a strong correlation between alcohol intake and carbohydrates, and herein particularly the intake of sucrose. To further investigate this relation the study examined consumption of candy and chocolates. Results of this study are summarized in Table 2. In women the intake of only candy was negatively related with alcohol intake (Spearmann r=-0.07, p<0.0001).

	Alcohol intake		
	0g/d	0.1-4.9g/d	>50g/d
Women			
Only candy	5.67 g/d	5.39g/d	2.48g/d
Candy + chocolate	3.12 g/d	3.12 g/d	3.40g/d
Men			
Only candy	1.98 g/d	1.70 g/d	0.85g/d
Candy + chocolate	1.98 g/d	1.70 g/d	0.85g/d
Chocolate	3.69 g/d	3.69 g/d	2.27 g/d

Table 2. Intake of alcohol vs. candy and chocolate in men and women (Adapted from Colditz *et al.* 1991).

Earlier studies have repeatedly documented that consumption of alcohol is associated with losses in tissue PUFA (Salen and Olsson, 1997; Lands *et al.* 1998).

4.1.1 Chronic alcoholics, dietary pattern and nutritional intake

In Germany and in most industrialized countries chronic alcohol abuse is not only one of the most important causes of nutritional disorders but also of changes in dietary habits (Aaseth *et al.* 1986; Addolorato, 1998; Suter *et al.* 1997). For instance, studies have reported that increased alcohol consumption is positively associated with an increased consumption of coffee, cheese, eggs, fish, meat whereas negative association was found with the intake of fruits and milk consumption (Kesse *et al.* 2001). Similar results were also reported by Toniolo *et al.* (1991) in regards to intake of fruit and dairy products. As mentioned above the results of Colditz *et al.* (1991) have reported that consumption of alcohol up to 50g/d was associated with lower intake of sugar in men. Results of Nanji et al. (1985) reported that pork and alcohol consumption were significantly correlated to cirrhosis mortality (r=0.98, p<0.001). A study by Bergheim et al. (2003) performed on German male middle-class alcohol consumers found that in chronic alcohol consumption protein intake is within the recommended daily allowances. However, the intake of fat and carbohydrate was lower in alcohol consumers in comparison to controls. No significant differences were found in the intake of vitamin B1, B2, B6 and vitamin C as well as retinol in chronic alcohol consumers and controls. These results were in contrast with studies performed in the United States.

Linangpunsakul *et al*. (2010) used the Third National Health and Nutritional Examination Survey (NHANES III) to examine an association between the nutritional intake and alcohol consumption in the United States. These data reveal that in both male and female participants the energy derived from carbohydrates, proteins and fat decreased with increased alcohol consumption. The subjects consumed less fat and protein with increased consumption of alcohol. This large population study concluded that alcohol has replaced nutrients particularly in terms of energy. Furthermore, the increased consumption of alcohol has an inverse relation with macronutrient intakes. Studies have also shown that in alcohol consumers hepatic zinc and vitamin A are found to be depleted due to poor dietary intake (Leo and Lieber, 1999). Taken together, the results gathered in the United States from the above studies differ from Europe, where alcohol was added to the diet but has not substituted nutrients from food sources.

5. Alcohol and vitamins

5.1 Fat soluble vitamins

Vitamin A: Vitamin A, which is vital for bone growth and normal eye function, is found to be deficient in patients with alcoholic cirrhosis (Lieber, 2003). Indeed, it has been found in human studies that patients with severe alcoholic liver disease have reduced levels of hepatic vitamin A (Ahmed *et al.* 1994). Interestingly, in these patients ß-carotene levels in the blood were found to be normal, indicating that liver disease may modify the ability of liver to convert ß-carotene to vitamin A (Ahmed *et al.* 1994). On the other hand, results of Manari *et al*. (2003) have indicated that chronic alcohol abusers without alcoholic liver disease have lower dietary intake of vitamin A than recommended by the reference nutrient intake. However, noteworthy results of Leo and Lieber (1982) showed that chronic alcohol administration in rats fed with vitamin A supplemented diet resulted in decrease of hepatic vitamin A levels. Thus, decreased levels of vitamin A in alcohol abuse may not be linked to reduced intake or malabsorption alone, suggesting that other mechanisms might be involved. Results of animal studies suggest that chronic ethanol ingestion has increased the peripheral vitamin A status and decreased hepatic vitamin A content (Leo *et al.* 1986; Leo and Lieber, 1988).

Vitamin D: Results of several human studies have reported that chronic alcohol abuse resulted in reduction of plasma 1,25 dihydroxyvitamin D3 levels, which is an active form of vitamin D3 (Lund *et al.* 1977; Laitinen and Valimaki, 1991; Laitinen *et al.* 1990). Similar reduction of plasma 1,25 dihydroxyvitamin D3 levels were also found in animal studies after chronic ethanol exposure (Turner *et al.* 1988). Reduction of circulating vitamin D levels in alcohol abusers may lead to reduced bone mass and lower calcium levels (Sampson, 1997; Keiver and Weinberg, 2003). Vitamin D is crucial in maintaining insulin levels and deficiencies may lead to altered glucose metabolism (Clark *et al.* 1981; Gedik and Akalin, 1986).

Vitamin E: Vitamin E is a well known anti-oxidant, whose metabolism is also altered in alcohol consumption (Drevon, 1991). Results of Bergheim et al. (2003) suggest that vitamin E consumption was markedly lower in patients with different stages of alcoholic liver disease. Furthermore, several animal and human studies suggest that consumption of alcohol reduces the hepatic stores of vitamin E (Bjorneboe *et al.* 1986, 1987, 1988a, 1988b). Indeed, rats fed with ethanol have increased hepatic α-tocopherol quinine levels, a product of α-

tocopherol oxidation, suggesting that ethanol promotes vitamin E degradation (Kawase *et al.* 1989).

5.2 Water soluble vitamins

Thiamine: Thiamine or vitamin B1 is essential for proper neurological and cardiovascular functioning (Wood and Breen, 1979). Thiamine is available as free thiamine (T), thiamine diphosphate ester (TDP 80%), thiamine triphosphate and thiamine monophosphate ester in the organism. Alcohol can inhibit the rate limiting mechanism of thiamine transport after its absorption from gastro-intestinal tract (Mancinelli and Ceccanti, 2009). In chronic alcohol abusers the concentrations of T and TDP were found to be reduced however, they were not related to liver injury (Mancinelli and Ceccanti, 2009). Furthermore, results of Manari *et al*. (2003) reported that 73% of the alcohol abusers have low thiamine intake in comparison to reference nutrient intake. Taken together, thiamine deficiency can be due to alcohol or malnutrition acting by itself or in combination.

Riboflavin: Riboflavin or vitamin B2 is an essential component of the cofactors flavin adenine dinucleotide and flavin mononucleotide. Riboflavin deficiency seems to be prevalent in alcoholics due to poor dietary intake (Manari *et al.* 2003). However, ethanol seems not to have an effect on riboflavin absorption (Pekkanen and Rusi, 1979).

Pyridoxine: Pyridoxine or vitamin B6 is an essential cofactor in amino acid metabolism. Studies have shown that 50% of alcohol abusers have lower circulating levels of pyridoxal-phosphate (PLP), an indicator of vitamin B6 status; this deficiency might be attributed to poor dietary intake and demolition of the vitamin by phosphotases (Lumeng and Li, 1974; Lumeng, 1978; Fonda *et al.* 1989). Acetaldehyde, a product of ethanol oxidation in chronic alcohol abusers displaces protein bound PLP and exposes PLP to destruction of phosphotases (Lumeng and Li, 1974; Lumeng, 1978). Alteration in the amino acid metabolism due to PLP deficiency might be an aspect in the development of alcoholic liver disease. Indeed, animal studies have reported that chronic PLP deficient diet leads to the development of mild fatty liver (French and Castagna, 1967).

Folic acid: Folic acid or vitamin B9 plays an important role in facilitating many body processes. Folic acid deficiency is common in chronic alcohol abuse. For instance, a British study on alcoholics has reported that most of the patients had megaloblastic anaemia in association with lower liver folate levels and lower red blood cells (Wu *et al.* 1975). The causes of the deficiency are still unclear; however, numeral mechanisms have been proposed together with lower intake of folate, reduced intestinal absorption of polyglutamyl folates, alteration in hepatic and renal folate homeostasis and augmented folate catabolism (Halsted *et al.* 1973; Tamura and Halsted, 1983; Halsted *et al.* 1971; McMartin *et al.* 1989; Shaw *et al.* 1989).

Cobalamin: Vitamin B12 deficiency in chronic alcohol abusers is rare due to large hepatic deposits (Klipstein and Lindenbaum, 1965). Results of Kanazawa and Herbert (1985) reported higher levels of plasma vitamin B12 in chronic alcohol abusers than in controls. However, analysis of the hepatic tissue confirmed that vitamin B12 concentration was significantly lower in chronic alcoholics than in controls. Therefore, it might be concluded that chronic alcohol ingestion affects hepatic cobalamin homeostasis but probably also that of other organs (Cravo and Camilo, 2000).

6. Alcohol and minerals and trace elements

Nutritional disturbances are assumed to remain among the most relevant medical problems in alcohol consumers (Aaseth *et al.* 1986; Addolorato, 1998; Suter *et al.* 1997) but it is still not clear whether chronic alcohol consumption *per se* results in malnutrition (Lieber, 2003; Leo *et al.* 1993; Leo and Lieber, 1999; Morgan and Levine, 1988). As reviewed by Lieber (2003), malnutrition and malsupplementation of certain micronutrients can be observed in alcohol abusers in the United States, whereas in another study dietary intake of German middle-class alcohol abusers with liver damage did not differ from that of control subjects consuming only very low amounts of ethanol (Bergheim *et al.* 2003). However, malsupplementation or an excessive intake of special micronutrients may contribute to the development of hepatic damage in alcoholic liver disease in single cases.

6.1 Iron

In contrast to other micronutrients iron is known to promote liver damage. Oxidative stress plays a key role in the pathogenesis of alcoholic liver diseases. By catalyzing the conversion of superoxide and hydrogen peroxide to hydroxyl radicals, iron can contribute to induce oxidative stress and, thus, induce liver cirrhosis in experimental settings in rats treated with ethanol (Tsukamoto *et al.* 1995). In other studies with rodents, iron also increased the hepatotoxicity caused by alcohol (Stal and Hultcrantz, 1993). Alcoholic liver diseases are often associated with an iron overload (Kohgo *et al.* 2008). Even mild to moderate alcohol consumption has recently been shown to increase the prevalence of iron overload (Ioannou *et al.* 2004). Iron has been shown to accumulate in Kupffer cells as well as in hepatocytes (Farinati *et al.* 1995; Ioannou *et al.* 2004). However, the mechanisms involved in the accumulation of iron in the liver when alcohol is ingested chronically are still poorly understood. Two possible mechanisms that are discussed to lead to an accumulation of iron in alcohol-inuced liver diseases are 1. an increased uptake of iron into hepatocytes, 2. an increased intestinal absorption of iron (Kohgo *et al.* 2008). In a study in Japanese patients with alcoholic liver disease it has been shown that the expression of transferrin receptor 1 was increased in hepatocytes (Suzuki *et al.* 2002) indicating that ethanol may increase iron uptake in hepatocytes. Another important factor that may be involved in iron overload found in patients with alcoholic liver disease is the systemic iron hormone hepcidin. Hepcidin plays an important role in duodenal iron absorption. In recent years it has been shown that hepcidin expression is downregulated in alcoholic liver disease (for overview see (Kohgo *et al.* 2008)).

6.2 Zinc

Zinc is an essential trace element and the daily recommended intake for adults ranges from 7 mg to 11mg. Zinc plays an essential role not only in catalytic reactions but also in the maintenance of the structural integrity of proteins by forming a "zinc finger-like" structure created by chelation centers, including cysteine and histidine residues (Klug and Schwabe, 1995) and in the regulation of gene expression. For example, metallothionein expression is regulated by a mechanism that involves the binding of zinc to the metal regulatory transcription factor 1, which in turn activates gene transcription (Cousins, 1994; Dalton *et al.* 1997). Zinc is necessary for the function of nearly 100 specific enzymes (e.g. alcohol dehydrogenase, retinol dehydrogenase) and is essential for macronutrient metabolism (e.g.

carbohydrate and protein metabolism), wound healing, the immune system, glucose control, growth, digestion, and fertility (King and Cousins, 2005; Prasad, 1995; Lipscomb and Strater, 1996). In alcoholic abusers, evidence of zinc deficiency has been reported repeatedly (Aaseth *et al.* 1986; Bjorneboe *et al.* 1988). Results of a study in German middle-class alcohol consumers indicated that zinc concentrations in plasma were significantly decreased in alcohol consumers with different stages of alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), whereas urinary zinc loss was increased in this patients (Bergheim *et al.* 2003). This is in line with the findings of previous studies, which reported decreased intestinal absorption of zinc (Valberg *et al.* 1985; Dinsmore *et al.* 1985) and increased zinc excretion in urine (Sullivan, 1962) being the most important reasons for zinc deficiency caused by alcohol consumption. Indeed, zinc deficiency is one of the most commonly observed nutritional manifestations of alcoholic liver disease (McClain *et al.* 1991). It has been discussed by Kang and Zhou (2005) that a supplementation of zinc may have a high potential to be developed as an effective agent in the prevention and treatment of alcoholic liver disease.

6.3 Copper

Copper plays an essential role as component of a number of metalloenzymes acting as oxidases (e.g cytochrome c oxidase). The daily recommended intake for adults ranges from 0.9 mg to 1.5 mg. In humans, an isolated copper deficiency rarely occurs and is normally due to an insufficient intake. However, the consumption of alcohol has been shown to be associated with a significant reduction of the levels of copper in serum (Schuhmacher *et al.* 1994). Results of a study in patients with alcoholic cirrhosis indicate that liver copper contents and urinary copper excretion were higher in cirrhotic patients and were related with the severity of chronic alcoholic liver disease (Rodriguez-Moreno *et al*., 1997). Besides zinc, copper is an essential cofactor of the copper/zinc superoxide dismutase, which is an enzyme that catalyzes the dismutation of superoxide into oxygen and hydrogen peroxide. In the liver, one of the most important antioxidants is the copper/zinc superoxide dismutase (Suter, 2005). In biopsies from patients with alcoholic liver disease it has been shown that the amount of copper/zinc superoxide dismutase reactivity was significantly lower than in control biopsies (Zhao *et al*., 1996).

6.4 Magnesium

As a cofactor for more than 300 enzyme systems (Wacker and Parisi, 1968) magnesium plays an essential role in anaerobic and aerobic energy generation and in glycolysis, being part of the Magnesium-ATP complex or acting as an enzyme activator (Garfinkel and Garfinkel, 1985). The daily recommended intake for adults is 300-400mg. Magnesium deficiency leads to many specific and unspecific symptoms such as anxiety, insomnia, nervousness, high blood pressure, and muscle spasms. Alcohol abusers are at high risk for magnesium deficiency because alcohol dose-dependently increases urinary excretion of magnesium (Laitinen *et al.* 1992). Even in cases of moderate alcohol consumption an increased excretion of magnesium in urine can be observed (Rylander *et al.* 2001). In dependence on the severity of alcohol abuse, 30 to 60% of alcoholics and nearly 90% of patients experiencing alcohol withdrawal have low magnesium levels in serum/plasma (Flink, 1986). The increased loss of magnesium may be potentiated by an insufficient intake or by an intestinal loss (e.g. through diarrhoea and vomiting).

6.5 Selenium

Selenium plays an important role as cofactor in several enzyme systems, such as the glutathione peroxidase, which acts as a cellular protector against free radical oxidative damage (Foster and Sumar, 1997). Low levels of selenium in plasma, serum or blood have not only been reported in patients with alcohol-induced cirrhosis but also in other liver diseases (for overview see McClain *et al.* (1991)). Results of a study in German middle-class alcohol consumers indicated that selenium concentrations in plasma and in erythrocytes were significantly decreased in alcohol consumers with different stages of alcoholic liver diseases compared to healthy controls, although the dietary intake of selenium was not decreased in these patients with alcoholic liver disease (Bergheim *et al.* 2003). In contrast, in other studies depressed serum selenium concentrations correlated closely with poor nutritional status (Tanner *et al.* 1986) and with the severity of alcohol-induced liver damage (Dworkin *et al.* 1985). In patients with alcohol-induced cirrhosis an additional decreased content of selenium in the liver was observed (Dworkin *et al.* 1988).

7. Clinical manifestation, diagnosis and therapy of malnutrition

As discussed in the previous sections of this chapter, alcohol consumption and herein particularly chronic intake of alcohol but also alcohol metabolism is associated with numerous alterations such as changes in dietary pattern (e.g. elevated intake of pork), impaired intestinal absorption of micro- but also macronutrients but also metabolism in the liver. As a consequence malnutrition is frequently found in patients with alcoholic liver disease. Indeed, as reviewed by Stickel *et al.* (2003), malnutrition can be both, a primary event resulting from a poor diet and decreased caloric intake but also a secondary process resulting from malabsorption and maldigestion. The question if the progression of alcoholic liver disease can be improved by nutritional support to these patients has been addressed in several clinical trails using oral, enteral, or parenteral routs to deliver nutritional formulas (for overview also see Halsted (2004; DiCecco and Francisco-Ziller (2006)). However, many of the studies were inconclusive as in some studies control groups were inadequate or control formulas were unbalanced, duration of studies was too short or nutritional needs were not adequately assessed (Halsted, 2004). In the following, methods for the assessment of nutritional status and recommendations for nutritional support of patients with alcoholic liver disease are briefly summarized (for overview also see Halsted (2004; DiCecco and Francisco-Ziller (2006; Plauth *et al.* (2006)).

7.1 Assessment of nutritional status

Assessing the nutritional status of a patient with alcoholic liver disease may be challenging as many of the traditional tools may be affected by the disease (e.g. body weight changes may stem from fluctuation in oedema or ascites). Indeed, diminished serum levels of hepatic protein such as albumin and transferrin may rather be indication of an altered protein biosynthesis in the liver than a protein caloric malnutrition (Fuhrman *et al*. 2004). In patients without fluid overload, midarm muscle area and creatinine excretion in urine have been shown to be the most reliable measures of nutritional status, whereas in those patients with ascites and oedema creatinine height index is more reliable (Nielsen *et al.* 1993). Furthermore, serum status of vitamins such as A, D, E, and folate as well as minerals like zinc and iron as well as skin turgor, poor oral health and temporal muscle wasting or night

blindness should also be assessed and may also help to identify losses of muscle mass and micronutrient deficiencies (Figueiredo *et al.* 2000). The subjective global assessment method, which combines subjective and objective measures has been found to accurately reflect the nutritional status of patients with end-stage liver disease (Hirsch *et al*. 1991, Hasse *et al.* 1993). Taken together, a detailed diet history, anthropometric measurements (e.g. triceps skinfold, arm circumference, body mass index), and measurements of handgrip strength but also measurements of vitamin and mineral status in serum are recommended when nutritionally assessing patients with alcoholic liver disease (DiCecco and Francisco-Ziller, 2006).

7.2 Oral nutritional supplementation

One of the first-line therapies to prevent and treat malnutrition in patients with alcoholic liver disease is through oral feeding including supplements. Herein, avoiding a fasting state, minimizing dietary restrictions, and offering small, frequent feedings is critical to meet the caloric and protein requirements (DiCecco and Francisco-Ziller, 2006). The benefit of oral nutritional supplementation has been assessed in many studies; however, due to poor study design or to small patients numbers included a final conclusion regarding the efficacy of this approach cannot yet be drawn. As reviewed by Stickel *et al.* (2003) and Halsted (2004) and stated in the guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN) on enteral nutrition for patients with liver disease (Plauth *et al.* 2006) oral nutritional supplements may improve nutritional status and complications of alcoholic liver disease and are recommend, although the true effect on survival is still unknown.

7.3 Enteral nutritional supplementation

Enteral tube feeding is second option to treat malnutrition in patients with alcoholic liver disease and is especially considered a save and efficient way to improve the nutritional status in those patients unable or willing to consume adequate oral nutrition. Indeed, despite the sometimes poor patient acceptance of the tube feeding it has been shown in several studies, that tube feeding may improve digestion but also has a short-term positive effect on liver function and may improve long-term survival (for overview also see Halsted, (2004; Plauth *et al.* (2006)).

7.4 Parenteral nutritional supplementation

The advantage of parenteral nutrition is the delivery of a precisely defined amount of protein, total calories, micronutrients, fluid, and electrolytes; however, clinical trails performed to evaluate the effect of parenteral nutrition in patients with alcoholic liver disease are difficult to interpret as study design was mostly inadequate (e.g. intake of controls was not adjusted, length of study, follow-up). The ESPEN guidelines advise that parental formula should provide adequate calories and protein with careful monitoring of glucose and electrolytes (Plauth *et al.* 2006).

8. Conclusion

Results of several studies suggest that quantity and frequency of alcohol consumption are important in the pathogenesis of alcoholic liver disease. Malnutrition is frequently present

in patients with alcoholic liver disease and may result from an altered dietary pattern, disturbed intestinal absorption and nutrient utilization in the liver due to the concomitant alcohol metabolism and/ or alcohol-induced impairments of liver function. Nutritional support including provision of adequate calories and protein but also micronutrients avoiding extended fasting periods and restricted diets may help to improve health status of patients with alcoholic liver disease; however, more clinical trails are needed to clarify the long-term effects of nutritional treatment on liver status and survival in patients with alcoholic liver disease.

9. References

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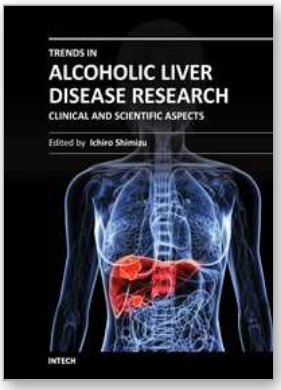

Trends in Alcoholic Liver Disease Research - Clinical and Scientific Aspects

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Alcoholic liver disease occurs after prolonged heavy drinking. Not everyone who drinks alcohol in excess develops serious forms of alcoholic liver disease. It is likely that genetic factors determine this individual susceptibility, and a family history of chronic liver disease may indicate a higher risk. Other factors include being overweight and iron overload. This book presents state-of-the-art information summarizing the current understanding of a range of alcoholic liver diseases. It is hoped that the target readers - hepatologists, clinicians, researchers and academicians - will be afforded new ideas and exposed to subjects well beyond their own scientific disciplines. Additionally, students and those who wish to increase their knowledge will find this book a valuable source of information.

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