IS NUTRIENT INTAKE A GENDER-SPECIFIC CAUSE FOR ENHANCED SUSCEPTIBILITY TO ALCOHOL-INDUCED LIVER DISEASE IN WOMEN?

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Abstract — Aim: Women have a higher susceptibility to alcohol-induced liver disease (ALD) than men. Gender-related differences in food preference were described in previous studies for several populations, but not in alcohol abusers. As certain micronutrients are reported to take influence on the development of ALD in animal experiments, the hypothesis of the present retrospective cross-sectional study was that gender-dependent (micro-) nutrient intake in patients with ALD may cause the higher susceptibility of women to this disease. Methods: In 210 patients (male: 158, female: 52) with different stages of ALD (ALD1: mild stage of liver damage; ALD2: moderately severe changes of the liver with signs of hepatic inflammation; ALD3: severely impaired liver function) and in 336 controls (male: 208, female: 128), nutrient intake was determined by a computer-guided diet history, and related to the severity of ALD in dependence on the sex of the patients. Results: No significant differences between males and females with ALD were calculated for the intake (per kg body weight/day) of protein, carbohydrates, fat, and the intake (per kg body weight/day) of most micronutrients. In females with ALD, higher intake was found for vitamin C (ALD3), calcium (ALD2), iron (ALD1 and ALD2), and zinc (ALD1), but the consumption of none of these micronutrients seems to contribute to a higher susceptibility to ALD in females. Conclusion: Though the present study confirms the higher susceptibility to ALD in women, the data of calculated daily macro- and micronutrient intake do not suggest any explicit influence of gender-specific nutrition in the development of ALD.

INTRODUCTION

The damage of the liver and other organs in consequence of chronic alcohol consumption is an important health problem in industrialized countries. A high number of people continue to die in the consequence of alcohol abuse (John and Hanke, 2002). Especially, chronic alcohol abuse is one of the most important risk factors for liver damage (Lieber, 1994). In previous studies, a close dose-response relation between alcohol intake and the risk of alcohol-induced liver disease (ALD) was demonstrated (Leblach, 1975; Day, 1997). Different severities of ALD such as alcohol-caused fatty liver, alcoholic hepatitis or alcohol-induced cirrhosis can be observed as a consequence of alcohol abuse, whereby women have an increased susceptibility to ALD as compared with men. Only half the average amount of alcohol consumed is assumed to be sufficient to cause comparable damage to health in females (Becker et al., 1996). It is also generally accepted that the incidence of alcohol-related chronic advanced liver disease is higher among women (Morgan and Sherlock, 1977) and that severe liver damage occurs earlier in life in female alcohol abusers (Tuyns and Pequignot, 1984). Besides, the lower body water content in women, which leads to higher relative ethanol concentrations compared to men after ingestion of equal amounts of ethanol, it has not been clarified whether the higher susceptibility to ALD in women is due to sex-related differences or to sex-associated behavioural (gender) dissimilarity. Sex differences do not only exist in the susceptibility to ALD but also in gender-specific nutritional behaviour and food preferences. Despite the fact that women are preferentially prone to ALD, they generally prefer a higher intake of food that they consider to be ‘healthy’ (i.e. more vegetable/fruits and less meat/fat) than men (Hoogerbrugge et al., 2001; Warde et al., 2004). These gender-related differences in food preference obviously correlate with a different pattern of (micro-) nutrient intake in men and women. A mis-balanced intake of some micronutrients was reported to contribute to the development of liver cell damage in studies with animals (Russell et al., 1974; Stal and Hultcrantz, 1993). Other studies documented beneficial effects of some micronutrients in ALD development (Lee et al., 1995; Cadenas et al., 1998; Kang and Zhou, 2005). As reviewed by Lieber (2003), malnutrition and mal-supplementation 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 negligible amounts of ethanol (Bergheim et al., 2003). However, mal-supplementation or an excess intake of special micronutrients may contribute to the development of hepatic damage in ALD in single cases.

The aim of the present study was to calculate the intake of some selected nutrients in male and female patients with ALD and to investigate whether there exist gender differences in macro- and micronutrient intake that might be responsible for the higher susceptibility of women to the development of ALD compared to men.

MATERIALS AND METHODS

Subjects
The study was approved by the Ethics Committee of the Robert-Bosch-Hospital, Stuttgart, Germany, and was carried...
and a γ time were in the normal range and AST in serum was
prised patients in whom bilirubin and relative prothrombin
cut off in accordance with the Helsinki Declaration of 1975, as
revised in 1983. All subjects gave their informed consent to
participate in the study. A total of 210 (male: 158, female: 52) hospitalized patients, who have consumed more than 60 g
alcohol/day for more than 3 years were included in the study.
All subjects displaying various stages of ALD and not having
abstained from alcohol for more than 3 days before admission
to the hospital were classified into three groups depending on
the severity of liver injury. In accordance to previous stud-
ies (Parlesak et al., 2000; Bergheim et al., 2003; Parlesak
et al., 2005), patients were divided into two groups without
cirrhosis (groups ALD1 and ALD2) and one group with cir-
rhosis (group ALD3). The diagnosis of alcohol-induced liver
cirrhosis was done by an experienced physician with ultra-
sound diagnosis and was confirmed either by liver biopsy or
by meeting typical clinical criteria: (i) the presence of ascites,
oesophageal varices or splenomegaly; and/or (ii) by meeting
two out of the following three criteria: relative prothrom-
bin time <60%, bilirubin plasma concentration >3.5 mg/dl
or serum albumin <2.5 g/dl, and (iii) the presence of one of
the following two criteria: aspartate aminotransferase (AST)
>40 u/l or γ-glutamyltransferase (γ-GT) >100 u/l (Table 1).
Alcohol abusers not meeting the criteria of cirrhosis were
assigned to group ALD2, if alanine aminotransferase (ALT)
in serum was >35 u/l and bilirubin was above 1.5 mg/dl, or
if AST in serum was >40 u/l. Additional criteria to meet
for patients in group ALD2 were an AST/ALT-quotient >1.0
and a γ-GT-activity in serum >55 u/l. Group ALD1 com-
prised patients in whom bilirubin and relative prothrombin
time were in the normal range and AST in serum was <40 u/l
and ALT in serum was <35 u/l. If patients agreed to a liver
biopsy, histological diagnosis was used in addition to assign-
ing patients to group ALD1 with the diagnosis ‘fatty liver’,
those with ‘alcoholic hepatitis’ to group ALD2, and those with
the classification ‘cirrhosis’ to group ALD3. Due to refusal
of patients, or a contraindication for biopsy sampling in con-
sequence of a reduced coagulation (i.e. in patients of group
ALD3), liver biopsies were obtained only from 53 patients
with ALD (ALD1: 13, ALD2: 24, ALD3: 16). However, in
all cases, the blind biopsy assessment confirmed the assign-
ment of alcoholic fatty liver to ALD1, alcoholic hepatitis
to ALD2, and alcoholic cirrhosis to ALD3. Therefore, the
probability of a classification not resulting in the histological
assignment ‘fatty liver’, ‘hepatitis’, and ‘cirrhosis’ to groups
ALD1–3, respectively, was less than 0.1% (P < 0.001; chi-
square test).
Exclusion criteria were age <18 and >61 years, preg-
nancy, acute pancreatitis, malignancies, cardiac decompen-
sation, bacterial infections, rheumatic diseases, surgery, blood
transfusion within the last 3 months, and hepatitis B or C
infection, diabetes mellitus, inflammatory bowel disease, mor-
bid obesity, limited mental capability, and hepatotoxic med-
ication. Three hundred and thirty-six subjects (male: 208,
female: 128), who consumed less than 20 g alcohol per day
served as controls (C). On the one hand, healthy volunteers
(staff of the hospital, co-workers in the laboratory) were asked
to participate in the study. On the other hand, subjects, who
were hospitalized for routine analyses because of intestinal
discomfort, but who were free from polyps >20 mm, diver-
ticulitis, ulcerative colitis, Crohn’s disease, diarrhea, liver
diseases, and all the general exclusion criteria mentioned
before, served as controls.

Table 1. Clinical, laboratory, and anthropometric parameters* of patients on admission and of healthy controls (C); patients with mild (ALD1), moderately severe (ALD2), and severe (ALD3) stages of alcohol-induced liver disease (ALD)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Healthy controls</th>
<th>Non-cirrhotic ALD</th>
<th>Cirrhotic ALD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>ALD1</td>
<td>ALD2</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>N</td>
<td>208</td>
<td>128</td>
<td>82</td>
</tr>
<tr>
<td>Age</td>
<td>44 ± 0.7</td>
<td>51 ± 0.7***</td>
<td>45 ± 1.0</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>79 ± 0.8</td>
<td>67 ± 1.1***</td>
<td>78 ± 1.8</td>
</tr>
<tr>
<td>BMI (kg/m²) 18 – 25</td>
<td>25 ± 0.2</td>
<td>25 ± 0.4</td>
<td>25 ± 0.5</td>
</tr>
<tr>
<td>AST (u/l) 2 – 19</td>
<td>12 ± 0.2</td>
<td>11 ± 0.6</td>
<td>24 ± 1.4</td>
</tr>
<tr>
<td>ALT (u/l) 5 – 24</td>
<td>16 ± 0.3</td>
<td>15 ± 0.5</td>
<td>26 ± 2.0</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>0.8 ± 0.01</td>
<td>0.8 ± 0.04</td>
<td>1.0 ± 0.06</td>
</tr>
<tr>
<td>γ-GT (u/l) 6 – 28</td>
<td>13 ± 0.6</td>
<td>11 ± 0.9</td>
<td>103 ± 19.7</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>0.9 ± 0.03</td>
<td>0.9 ± 0.09</td>
<td>1.0 ± 0.06</td>
</tr>
<tr>
<td>0.2 – 1.4</td>
<td>93 ± 0.5</td>
<td>95 ± 1.4</td>
<td>92 ± 1.6</td>
</tr>
<tr>
<td>Relative prothrombin</td>
<td>93 ± 0.5</td>
<td>95 ± 1.4</td>
<td>92 ± 1.6</td>
</tr>
<tr>
<td>time (%) 70 – 100</td>
<td>4 ± 0.03</td>
<td>4.4 ± 0.15</td>
<td>4.2 ± 0.11</td>
</tr>
</tbody>
</table>

*P < 0.05; †P < 0.01; ††P < 0.001 females versus males within one group; calculated by two-way-ANOVA and post-hoc test of Tukey.
†P < 0.05; ††P < 0.01; †††P < 0.001 females with ALD versus female controls and males with ALD versus male controls respectively; calculated by
two-way-ANOVA and post-hoc test of Tukey (for parameters that were used for classification of ALD significant differences between males/females with
ALD and male/female control subjects were not denoted).
*All data expressed as mean ± SEM; †Normal range; †Percentage of normal values; AST, aspartate aminotransferase; ALT, alanine aminotransferase;
γ-GT, gamma-glutamyltransferase.
Both cases (within 3 days after admission) and controls were nutritionally assessed by a trained nutritionist using a computerized, established method of obtaining a detailed retrospective diet history, which has been validated previously (Landig et al., 1998). To eliminate seasonal variation in nutritional behavior, study participants were asked about their average long-term nutrition pattern (past 3–6 months). The program of this method is based on the German food and nutrient database (Bundeslebensmittelschlüssel, BLS). This database includes more than 11 000 food items and recipes. To improve the estimation of their usual portion size for each item, subjects were provided with photographs of small, medium, or large serving sizes of the most frequently consumed foods. Also, the intake of vitamin/mineral supplements was considered. To avoid bias of the reported alcohol intake, study participants were asked about their average daily food intake without focusing on the consumption of alcoholic beverages. Nevertheless, during obtaining the diet history, subjects and controls were asked about their frequency of alcohol consumption and serving size in terms of medium glasses or bottles of wine, 0.3 l cans or bottles of beer or shots of hard liquor. For calculation of mean daily alcohol consumption, the following alcohol concentrations (v/v) were assumed: beer 4%, wine 11%, hard liquors 40%.

Statistical analysis

All results are given as mean ± SEM (standard error of the mean). Analysis of variances (two-way-ANOVA: gender and severity of ALD) with the consequent post-hoc test of Tukey were applied for the determination of significance levels (Statistica Version 6.0 software, StatSoft, Inc., Tulsa, USA). Value distributions within the single groups were checked for homogeneity of variances (Bartlett’s test) to meet the requirements for applicability of ANOVA. Student’s t-test was applied for comparisons of quintiles of different nutrient intake. Differences were considered as significant if the P value was less than 0.05.

RESULTS

Clinical diagnoses, laboratory findings, and anthropometrical characteristics of subjects and controls are summarized in Table 1. In all groups (C, ALD1–ALD3), the mean body weight of women was lower (Table 1). As expected, due to the classification criteria of all ALD groups, the tests indicating an impaired liver function and liver damage (bilirubin, albumin, relative prothrombin time, AST, ALT, γ-GT, and AST/ALT) were not within the normal range in most ALD groups, depending on the severity of ALD (Table 1). In female patients with more advanced stages of ALD, significantly higher values for AST/ALT ratio (ALD2 and ALD3) and γ-GT (ALD2) were measured compared to male patients (Table 1), indicating a more severe liver damage in women compared to men at comparable or lower alcohol consumption, regarding both the absolute daily alcohol intake and the relative daily alcohol intake per kg of body weight (Table 2).

Table 2. Daily intake of energy, alcohol, fat, protein, and carbohydrate in patients with mild (ALD1), moderately severe (ALD2), and severe (ALD3) stages of alcohol-induced liver disease (ALD), and in control subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Healthy controls</th>
<th>Non-cirrhotic ALD</th>
<th>Cirrhotic ALD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Alcohol (g/day)</td>
<td>9 ± 0.5</td>
<td>5 ± 0.5</td>
<td>142 ± 12.6</td>
</tr>
<tr>
<td>Alcohol (g/kg body weight/day)</td>
<td>0.12 ± 0.01</td>
<td>0.09 ± 0.01</td>
<td>1.9 ± 0.19</td>
</tr>
<tr>
<td>Total energy (kcal/day)</td>
<td>2636 ± 34</td>
<td>2232 ± 58**</td>
<td>3812 ± 189***</td>
</tr>
<tr>
<td>Energy without alcohol (kcal/day)</td>
<td>2571 ± 34</td>
<td>2193 ± 58***</td>
<td>2807 ± 153</td>
</tr>
<tr>
<td>Protein (g/day)</td>
<td>98 ± 1.6</td>
<td>81 ± 2.0***</td>
<td>101 ± 5.7</td>
</tr>
<tr>
<td>Protein (g/kg body weight/day)</td>
<td>1.24 ± 0.02</td>
<td>1.25 ± 0.03</td>
<td>1.36 ± 0.10</td>
</tr>
<tr>
<td>Fat (g/day)</td>
<td>113 ± 2.0</td>
<td>91 ± 2.9***</td>
<td>111 ± 6.7</td>
</tr>
<tr>
<td>Fat (g/kg body weight/day)</td>
<td>1.44 ± 0.02</td>
<td>1.40 ± 0.05</td>
<td>1.50 ± 0.11</td>
</tr>
<tr>
<td>Carbohydrates (g/day)</td>
<td>282 ± 4.6</td>
<td>250 ± 8.5</td>
<td>335 ± 19.6***</td>
</tr>
<tr>
<td>Carbohydrates (g/kg body weight/day)</td>
<td>3.61 ± 0.06</td>
<td>3.82 ± 0.14</td>
<td>4.56 ± 0.33</td>
</tr>
</tbody>
</table>

* P < 0.05; ** P < 0.01; *** P < 0.001 female versus male within one group; calculated by two-way-ANOVA and post-hoc test of Tukey.
† P < 0.05; †† P < 0.01; ††† P < 0.001 females with ALD versus female controls and males with ALD versus male controls respectively; calculated by two-way-ANOVA and post-hoc test of Tukey (for parameters that were used for classification of ALD significant differences between males/females with ALD and male/female control subjects were not denoted).

* All data expressed as mean ± SEM. ALD, alcohol-induced liver disease.
Both, female controls and female patients with ALD, had a significantly lower total energy intake per day than their male counterparts. No significant differences between women with ALD and healthy women were calculated for total energy intake, whereas male subjects of groups ALD1–ALD3 had a significantly higher total energy intake than male controls (Table 2). After excluding energy intake resulting from alcohol consumption, neither the energy intake of male patients nor that of female patients with ALD differed significantly from that of the male or female control subjects, respectively. Hence, an addition, but no substitution of energy intake through alcohol occurred in alcohol abusers. No significant differences in relative daily protein, fat, and carbohydrate intake were noted between men and women with different stages of ALD (Table 2).

The recorded daily intake of a few micronutrients was below the recommended dietary reference intakes (DRI) (Panel on Micronutrients, 2002; Panel on Dietary Reference Intakes for Electrolytes and Water, 2005). In detail, the intake of the micronutrients vitamin E (59–90%), thiamine (89–128%), folate (33–75%), potassium (67–90%), and calcium (88–128%) was at least partly below the DRI. The rest of the recorded (micro-) nutrient intakes was above the DRI and ranged between 102 and 370% in all sub-groups (data not shown).

Compared to male control subjects, male patients of group ALD1 had a significantly higher intake of riboflavin, vitamin B6, folate, potassium, magnesium, and phosphorus (Table 3). In contrast, females of group ALD1 ingested more phosphorus, iron, and zinc than female controls. Male patients with a moderately severe stage of ALD (ALD2) consumed more vitamin B6 and folate, but less calcium than male control subjects. Female subjects of group ALD2 differed from female controls by a lower intake of vitamin A and a higher intake of iron. In group ALD3, both men and women ingested more folate than male and female controls, respectively. (Table 3)

Comparing male and female subjects within the single ALD sub-groups, females consumed significantly more iron (ALD1, ALD2), zinc (ALD1), calcium (ALD2), and vitamin C (ALD3) than the corresponding male counterparts. (Table 3)

Neither male nor female patients belonging to the quintile with the lowest or highest intake of iron differed significantly in respect to all applied indicators of ALD (AST, ALT, γ-GT, AST/ALT ratio, bilirubin, albumin, relative prothrombin time). Regarding the daily intake of zinc, none of the indicators of ALD differed significantly between patients belonging to the quintile with the lowest intake of zinc and those belonging to the quintile with the highest intake (Table 3).

## DISCUSSION

A higher susceptibility to ALD in female alcohol abusers has been evidenced by different previous studies referring to an accelerated development of ALD in women than in men at a comparable alcohol consumption (Ashley et al., 1977; Loft et al., 1987; Schenker, 1997) and to the lower amount of consumed alcohol that is needed to cause comparable health damage in females (Becker et al., 1996). These findings correspond to results of the current study in which female alcohol abusers had a significantly higher AST/ALT ratio (suggesting a more severe stage of alcohol-induced liver cell damage) than their male counterparts, although they tended

### Table 3. Daily micronutrient intake (per kg of body weight/day) in patients with mild (ALD1), moderately severe (ALD2), and severe (ALD3) stages of alcohol-induced liver disease (ALD) and healthy control subjects (C)

<table>
<thead>
<tr>
<th>Micronutrients</th>
<th>Healthy controls</th>
<th>Non-cirrhotic ALD</th>
<th>Cirrhotic ALD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Vitamin A (µg/kg/d)</td>
<td>11.9 ± 0.5</td>
<td>21.7 ± 1.3***</td>
<td>16.5 ± 1.9</td>
</tr>
<tr>
<td>Vitamin E (mg/kg/d)</td>
<td>0.17 ± 0.01</td>
<td>0.20 ± 0.01*</td>
<td>0.16 ± 0.01</td>
</tr>
<tr>
<td>Thiamin (µg/kg/d)</td>
<td>19.4 ± 0.4</td>
<td>20.2 ± 0.6</td>
<td>20.7 ± 1.4</td>
</tr>
<tr>
<td>Riboflavin (µg/kg/d)</td>
<td>22.8 ± 0.4</td>
<td>24.4 ± 0.8</td>
<td>32.7 ± 2.1***</td>
</tr>
<tr>
<td>Folate (µg/kg/d)</td>
<td>24.1 ± 0.4</td>
<td>26.6 ± 0.8</td>
<td>35.2 ± 2.1***</td>
</tr>
<tr>
<td>Magnesium (mg/kg/d)</td>
<td>68.8 ± 1.5</td>
<td>55.5 ± 5.8</td>
<td>62.1 ± 5.3</td>
</tr>
<tr>
<td>Potassium (mg/kg/d)</td>
<td>43.9 ± 0.7</td>
<td>50.8 ± 1.4***</td>
<td>57.1 ± 3.4***</td>
</tr>
<tr>
<td>Calcium (mg/kg/d)</td>
<td>17.1 ± 0.4</td>
<td>17.1 ± 0.6</td>
<td>14.4 ± 1.3</td>
</tr>
<tr>
<td>Magnesium (mg/kg/d)</td>
<td>6.3 ± 0.1</td>
<td>6.6 ± 0.2</td>
<td>8.2 ± 0.5***</td>
</tr>
<tr>
<td>Phosphorus (mg/kg/d)</td>
<td>22.0 ± 0.4</td>
<td>20.4 ± 1.7</td>
<td>29.3 ± 2.1***</td>
</tr>
<tr>
<td>Iron (mg/kg/d)</td>
<td>0.20 ± 0.00</td>
<td>0.22 ± 0.01</td>
<td>0.21 ± 0.01</td>
</tr>
<tr>
<td>Zinc (mg/kg/d)</td>
<td>0.18 ± 0.00</td>
<td>0.18 ± 0.01</td>
<td>0.16 ± 0.01</td>
</tr>
</tbody>
</table>

* P < 0.05; ** P < 0.01; *** P < 0.001 male versus female within one group; calculated by two-way-ANOVA and post-hoc test of Tukey.

1 P < 0.05; †† P < 0.01; ††† P < 0.001 females with ALD versus female controls and males with ALD versus male controls respectively; calculated by two-way-ANOVA and post-hoc test of Tukey. All data expressed as mean ± SEM.
to consume less alcohol per day (significant only in group ALD1).

Already, in children aged 4 to 16 years, gender-related differences in nutritional behaviour can be observed (Cooke and Wardle, 2005), suggesting a different pattern of nutrient intake in both sexes. However, no noteworthy differences in macronutrient intake (protein, fat, carbohydrates) between male and female patients with different stages of ALD were measured in the present study. This suggests that none of these macronutrients is likely to play a major role in a higher susceptibility to ALD in females than in males.

Sodium, potassium, calcium, magnesium, and phosphorus were so far neither considered to be involved in the development of hepatic cell damage induced by alcohol nor were noteworthy in being differently consumed by male and female subjects with ALD in the present study. These findings suggest that these micronutrients do not play an essential role in the differential development of liver damage in male and female patients with ALD.

In contrast, some other micronutrients were reported to have either beneficial effects or the lack of them to lead to noticeable histological or functional adverse changes of the liver, such as Vitamin E (Lee et al., 1995), zinc (Kang and Zhou, 2005), folate (Halsted et al., 2002), vitamin C (Cadenas et al., 1998), vitamin B6 (Tayss, 2005), and riboflavin (Manthey et al., 2006). In the current study, no differences between men and women with ALD were found for the daily intake (per kg body weight) of vitamin E, folate, riboflavin, and vitamin B6 suggesting that the hepatoprotective effect of none of these micronutrients plays an essential role in the different susceptibility to ALD between men and women. Female patients of group ALD1 and ALD3 had a higher daily intake of zinc and vitamin C, respectively, making a zinc or a vitamin C mal-supplementation also an unlikely candidate for the higher susceptibility of women to ALD. Furthermore, neither in male nor in female subjects of quintiles with the highest or lowest intake of zinc, significant differences were calculated for any variable representing liver malfunction (AST, ALT, AST/ALT, γ-GT, albumin, bilirubin, prothrombin time). This indicates that the higher intake of zinc in female patients of group ALD1 has no influence on the higher susceptibility to ALD in women.

Other micronutrients such as vitamin A (Wormer et al., 1988) and iron (Stal and Hultcrantz, 1993) are known to promote alcohol-induced liver damage. In the present study, the daily intake of vitamin A did not differ between male and female subjects of all ALD groups. Females of groups ALD1 and ALD2 had a higher iron intake (per day and kg body weight) than male subjects of respective ALD groups. However, neither male nor female patients with ALD from quintiles of highest and lowest consumption of iron differed significantly with respect to indicators of ALD such as AST, ALT, AST/ALT, γ-GT, albumin, bilirubin, and prothrombin time. These findings indicate that neither the consumption of vitamin A nor that of iron plays an essential role in the higher susceptibility of women for ALD.

The non-existing distinct difference in nutrient intake does not necessarily mean that the investigated (micro-) nutrients do not play an essential role in sex-specific development of ALD. Both the intestinal absorption (Pfeiffer et al., 1993) and metabolism of (micro-) nutrients are affected by alcohol abuse (Lieber, 2000; Wagnerberger et al., 2006). To the best of our knowledge, no information on sex-specific differences in intestinal absorption is available; a topic needing attention in future studies. However, though there seems to be only a minor effect of a different nutrient intake by men and women on the heterogenic development of ALD in patients of both sexes (Himmelstein, 1983; Nanji and French, 1987; Becker et al., 1996), the hormonal background of this difference is without doubt. Female rodents exhibit a higher susceptibility to ALD (Imuro et al., 1997). This difference is thought to depend on estrogen (Yin et al., 2000), a heterogenic production of chemokines (Yamada et al., 1999), and an inhomogeneous susceptibility of Kupffer cells and hepatocytes towards stimulation with bacterial toxins (Thurman, 2000; Gallucci et al., 2004).

In conclusion, the present study confirms the higher susceptibility to ALD in women, but the data of calculated daily macro- and micronutrient intake of male and female subjects with different stages of ALD do not suggest any explicit influence of gender-specific nutrition in the development of ALD. Though significant differences exist between men and women with ALD with respect to the daily intake of certain micronutrients in some ALD sub-groups, these micronutrients are unlikely to be responsible for a higher susceptibility to ALD in females alone.

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REFERENCES


