

## Occasional Review

# Do women develop alcoholic liver disease more readily than men?

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### Abstract

**The sudden increase in alcoholic liver disease among women in the past 10 years has caused much speculation that they may be more susceptible to the hepatotoxic effects of alcohol than men. Women tend to present with more severe liver disease, particularly alcoholic hepatitis, and do so after a shorter period of excessive drinking and at a lower daily alcohol intake. Differences in body size and composition are partly responsible for the greater susceptibility of women, but differences in immune reactivity between the sexes may also play a part. Greater emphasis must be placed on designing abstinence programmes specifically for female patients, on earlier detection of liver disease, and on educating women about hazardous drinking levels.**

### Introduction

In the past decade the number of women in Britain, particularly young women, succumbing from alcoholic liver disease has risen dramatically.<sup>1</sup> This fact and the impression that many have been social drinkers only has caused much speculation as to whether women are more susceptible to the hepatotoxic effects of alcohol than men.

In view of the greater social acceptability of alcohol consumption by women and the wider availability of alcoholic drinks in retail outlets such as supermarkets, the possibility that women are predisposed to alcohol-induced liver damage is of considerable public-health importance. We therefore reviewed published reports on this topic to see whether special emphasis on the management and prevention of alcoholic liver disease in women is needed.

### An increasing problem

Twenty years ago alcoholic cirrhosis was a disease of middle-aged and elderly men. In reports from both district hospitals and specialist units covering the years from 1959 to the early 1970s men outnumbered women by nearly 5:1.<sup>2-4</sup> In the past 10 years the male to female ratio has fallen to about 2:1.<sup>4-7</sup> Four times as many women were admitted to hospital with

alcoholic cirrhosis in England and Wales in 1977 as in 1970,<sup>1</sup> and in Britain as a whole over 3000 women a year are admitted with alcoholic liver disease.

This increased frequency has followed a substantial increase in the consumption of alcoholic drinks by women over this period. Although population surveys have shown only a slight increase of about 12% in the per capita alcohol intake of women,<sup>8</sup> market research studies have shown that women are now drinking twice as much alcohol in the form of fortified wines and spirits as they did 10 years ago.<sup>9,10</sup> With this rise in consumption, there has been an increase in other alcohol-related problems among women. Between 1970 and 1978 convictions for drunkenness rose by 64%, the number of hospital admissions for treatment of alcoholism or alcoholic psychosis by 137%, and the death rate from alcoholism by 130%.<sup>11</sup> In each case the increase was considerably greater for women than for men.

### Are women at greater risk of liver damage than men?

The increased frequency of alcoholic liver disease among women is therefore not surprising, but the extent of the increase over the past 10 years is far greater than one would predict from the change in frequency of other alcohol-related problems. In addition, proportionately more women are treated for alcoholic liver disease than one would expect from the ratio of male to female alcohol abusers in the general population. Five to 10 times as many men as women are problem drinkers,<sup>12,13</sup> in contrast to the 2:1 ratio for those with liver disease. Despite problems in identifying heavy drinkers in population samples, this does suggest that women may develop alcohol-induced liver damage when consuming smaller quantities of alcohol than men, and that dependence on alcohol may not be a *sine qua non* for liver damage to occur.

It is difficult to establish whether women in general are at greater risk of developing alcoholic liver disease since over half the number of heavy drinkers never seek treatment<sup>14</sup> and the extent of their liver disease may never be known. Thus studies must be confined to those who have presented for treatment of their alcoholism or liver disease. There are two main approaches: firstly, comparative studies of the histological severity of liver damage among male and female alcoholics; and, secondly, analysis of the alcohol intake of patients with established alcoholic liver disease.

### Are there different disease patterns in men and women?

The finding that female alcoholics have more severe liver disease than their male counterparts<sup>4,5,15-18</sup> (table I) must be interpreted with some caution because differences in the severity of liver damage between the sexes might simply reflect

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different grounds for referral. For example, men are more likely to undergo medical examination for employment or insurance purposes and be referred if liver disease is suspected, whereas women may present only when symptoms have appeared. In a recent British study 22% of the male patients were referred because of asymptomatic hepatomegaly or abnormal liver function test results found at routine screening, compared with only 9% of the women.<sup>5</sup> Relatively more women than men (85% v 65%) had advanced liver disease—alcoholic hepatitis or cirrhosis—but this was probably accounted for by the fewer women who were identified at routine screening.

Since liver biopsy is the only reliable method of diagnosing and excluding alcoholic liver disease, information may be misleading unless all patients in a series undergo biopsy. Among 800 alcoholics who presented to an alcoholism clinic in Australia, cirrhosis was diagnosed in a significantly higher proportion of women than men (16.8% v 8.1%,  $p < 0.01$  by  $\chi^2$  analysis),<sup>15</sup> but a subsequent report from the same group of a consecutive series of 100 patients who underwent routine liver biopsy showed that the proportion of women with liver disease was only marginally higher.<sup>16</sup>

Two other series in which all patients underwent liver biopsy have shown that women are more likely to have serious liver disease, particularly alcoholic hepatitis. In an early study from Boston, USA, Phillips and Davidson<sup>17</sup> found that of 20 female alcoholics, 14 (70%) had the typical histological lesion of liver cell necrosis, polymorph infiltration, and Mallory's hyaline, compared with 41.2% of the men. In a more recent report from the liver unit, King's College Hospital, the most severe form of alcoholic hepatitis, central sclerosing hyaline necrosis, occurred in 11.5% of women and in only 3.3% of the men.<sup>4</sup>

Other studies of patients with alcoholic hepatitis also show a predominance of women: Lischner *et al*<sup>19</sup> found that 64% of their patients were women, significantly more than would be expected from the general medical admission rate, and in a British series of 258 patients a higher proportion of women than men had alcoholic hepatitis.<sup>20</sup>

No sex difference in the frequency of alcoholic hepatitis was found, however, in a large group of patients admitted to a

district general hospital in London, though more women than men tended to have established cirrhosis.<sup>18</sup> Nevertheless, the overall impression is that at presentation women do have relatively more severe liver disease.

**Alcohol intake and the risk of liver damage**

A quantitative relation between the amount of alcohol consumed and the degree of liver damage was first established by Leibel.<sup>21</sup> Unfortunately, in this study, the most comprehensive of its kind, women were not included. In a group of over 300 male alcoholics in whom liver histology was available there was a linear relationship between cumulative lifetime alcohol intake, corrected for body weight, and the likelihood of having cirrhosis.

In other studies of this type,<sup>4 5 7 15 18 22</sup> where both men and women have been interviewed, two measures of alcohol consumption have been used: the mean daily intake and the duration of excessive drinking (table II). Wilkinson *et al*<sup>15</sup> found that women with cirrhosis attending an alcoholism clinic in Australia had a mean daily intake of  $140 \pm 55$  g ( $\pm$ SD), two-thirds that of the men ( $210 \pm 80$  g,  $p < 0.01$ ). Part of this difference may be explained by the 15-20% lower body weight of women<sup>23</sup>; when, in that study, alcohol intake was corrected for body weight, the difference was not statistically significant.<sup>15</sup> Three other studies<sup>4 7 18</sup> also showed that women with alcoholic liver disease drank less than men, but in none of them was intake corrected for body weight.

The duration of excessive drinking is usually easier to ascertain than mean daily alcohol intake, and women drink for a shorter time before presenting with liver disease (table II).<sup>5 15 18 22</sup> With excessive drinking defined as 100 g alcohol/day or more, Wilkinson *et al*<sup>15</sup> found that women with alcoholic cirrhosis had drunk excessively for a mean period of  $13.5 \pm 8.4$  years, compared with  $20.0 \pm 9.5$  years for men with cirrhosis. All grades of liver damage seem to develop more rapidly. In a Canadian study both fatty liver and cirrhosis occurred after a shorter period of "hazardous drinking" ( $>80$  g alcohol/day) in women, although for the group with cirrhosis the difference

TABLE I—Analysis of studies comparing the percentage of male and female alcoholics with alcoholic hepatitis or cirrhosis

Authors	Clinical setting	No of patients		Equal proportions of asymptomatic men and women	All patients biopsied?	Histological lesion	% Men with lesion	% Women with lesion	$\chi^2$ analysis
		Male	Female						
Wilkinson <i>et al</i> <sup>15</sup>	Alcoholism unit	663	137	Yes	No	Cirrhosis	7.5	15.3	$p < 0.01$
Bhathal <i>et al</i> <sup>16</sup>	Alcoholism unit	77	23	Yes	Yes	Hepatitis ± cirrhosis	28.5	34.8	NS
Phillips and Davidson <sup>17</sup>	General hospital	34	20	Not stated	Yes	Hepatitis ± cirrhosis	41.2	70.0	$p < 0.05$
Levi and Chalmers <sup>18</sup>	General hospital	144	58	Yes	Yes	Hepatitis	7.6	5.2	NS
Krasner <i>et al</i> <sup>4</sup>	Specialist liver unit	215	78	Yes	Yes	Cirrhosis ± hepatitis	20.1	25.8	NS
						Hepatitis	12.6	15.4	NS
						Central hyaline necrosis	3.3	11.5	$p < 0.025$
						Cirrhosis + hepatitis	32.6	44.9	$p < 0.01$
Morgan and Sherlock <sup>5</sup>	Specialist liver unit	77	23	No	All except 3	Cirrhosis - hepatitis	24.2	16.7	NS
						Hepatitis	10.7	13.6	NS
						Cirrhosis ± hepatitis	54.7	72.7	$p < 0.1$

NS = Not significant.

TABLE II—Alcohol intake of men and women with alcoholic liver disease

Authors	No of patients		Severity of liver damage	Mean daily alcohol intake (g)		p	Duration of excessive drinking (yr)		p
	Male	Female		Men	Women		Men	Women	
Wilkinson <i>et al</i> <sup>15</sup>	54	23	Cirrhosis	210	140	$< 0.01$	20.0*	13.5*	$< 0.01$
Saunders <i>et al</i> <sup>7</sup>	184	58	Cirrhosis	152	112	$< 0.02$			
Krasner <i>et al</i> <sup>4</sup>	215	78	Mostly hepatitis or cirrhosis	91% >	65% >	$< 0.005$			
Morgan and Sherlock <sup>5</sup>	77	23	Mostly hepatitis or cirrhosis				20.4*	16.8*	NS
							20.4†	13.6†	$< 0.01$
Ashley <i>et al</i> <sup>22</sup>	372	38	Fatty liver				19.3†	17.4†	NS
Levi and Chalmers <sup>18</sup>	127	41	All grades				16.5†	8.9†	$< 0.001$
							44% >	27% >	$< 0.05$
					160	160			

\* - 100 g/day. † > 80 g/day. NS = Not significant.

was not statistically significant.<sup>22</sup> One explanation may be that women tend to drink more regularly than men, but in the above studies most patients of either sex with established cirrhosis had an unremitting pattern of daily drinking.

The case-control method of determining hazardous intake levels was pioneered by the French epidemiologist, Pequignot. In an early study<sup>24</sup> patients diagnosed as having alcoholic cirrhosis and an age-sex matched control group of hospital patients without liver disease were divided into three categories according to their daily intake of alcohol: <80 g, 80-160 g, and >160 g. Only one of the 116 patients with cirrhosis, compared with 59 of the controls, drank less than 80 g, which was suggested as the minimum intake that would put someone at risk of developing cirrhosis. Sixty-four patients with cirrhosis but only seven controls drank more than 160 g/day. Most cirrhotic patients in the intermediate group were women, whereas in the control group they were predominantly men, suggesting that the risk of developing cirrhosis with an alcohol intake of 80-160 g/day was considerably higher for women than for men.

As the use of hospital controls may be criticised because their alcohol intake is not necessarily representative of that of the whole population Pequignot and his co-workers<sup>25</sup> compared the alcohol intake of patients with cirrhosis of alcoholic or undetermined aetiology living in a certain area of France with that of healthy subjects drawn at random from the electoral register. For each category of alcohol consumption, the "cirrhosis morbidity quotient" (the ratio of the total number of cirrhotic patients to healthy subjects in the population sampled) was calculated. Results showed that women were at greater risk of cirrhosis if their daily alcohol intake exceeded 20 g and that men were at greater risk with an intake over 60 g, although the risk for women drinking 20-40 g/day and for men drinking 60-80 g/day was only slightly increased.

If women really do run a risk of cirrhosis at relatively low intakes of alcohol such as these, the implications are serious; however, these "hazardous" intake levels may be artificially low. Only three women in the control group consumed over 60 g/day, which suggests that the number of women in this category may not have been satisfactorily ascertained. In addition cases of cryptogenic cirrhosis were included in this study, which could give an artificially low estimate for the amount of alcohol necessary to produce liver damage. Even so, susceptibility to alcohol differed considerably between the sexes: the risk of cirrhosis for women drinking 60-80 g alcohol a day was at least 35 times greater than that for men. Unfortunately, because of the design of the study, it was not possible to determine for how long someone would have to drink these amounts before developing cirrhosis.

Women have often been described as secretive drinkers, and one concern is that they may tend to conceal their true alcohol consumption. Studies on the reliability of self-reported alcohol consumption, however, show a close correlation with information obtained from collateral sources and on retest when the interview is conducted in private.<sup>26-27</sup> Although no formal validation procedure was included in any of the clinical studies described above, corroborative evidence of the patient's alcohol consumption was available from relatives in many cases.

### Sex-related differences in prognosis

Since alcoholic liver disease develops more rapidly in women, its progression may also be quicker. An early study, in which women with cirrhosis were found to be eight years younger at death than male patients, supported this suggestion.<sup>28</sup> Most recent studies, however, have not found any significant difference in prognosis between male and female patients.<sup>29-31</sup> In a follow-up study of 278 patients with alcoholic cirrhosis, Powell and Klatskin<sup>29</sup> found that of those who abstained, 59% of the women and 66% of the men survived five years. In the group who continued to drink the five-year survival rates were

38% and 43% respectively. Neither of these differences is statistically significant.

One British study<sup>4</sup> reported a much worse outlook for women with alcoholic hepatitis or cirrhosis who continued to drink than for their male counterparts. Only 30% of the women survived five years compared with 72% of the men, but their liver disease was more severe at presentation, which could account for part of the subsequent difference in prognosis.

Women have long been regarded as more difficult to treat than men. A past history of psychiatric illness, usually depression, is more common in female alcoholics.<sup>32-33</sup> Relatively little information is available, however, on the proportions of men and women with alcoholic liver disease who abstain from alcohol after discharge from hospital. Powell and Klatskin<sup>29</sup> found that 34% of men and 33% of women stopped drinking, and in an Australian study slightly more women abstained after discharge.<sup>31</sup> In a British study, however, only 9% of women stopped drinking compared with 29% of men.<sup>5</sup> More data are available on the prognosis for women alcoholics without liver disease: in a recent review of 23 reports comparing the results of treatment in men and women Annis<sup>34</sup> found no overall difference between the sexes in the proportion of patients who stopped drinking.

### Are different pathogenetic mechanisms operative in men and women?

As alcoholic liver disease develops more rapidly and at a lower daily intake in women different pathogenetic mechanisms may be responsible. Evidence is accumulating that, in addition to the direct hepatotoxic effects of alcohol, immunological reactions directed against host liver cells play a part in the development of alcoholic liver disease.

Both humoral and cell-mediated immune reactions have been detected in patients with alcoholic liver disease, particularly alcoholic hepatitis, and may form the basis for a sex-related difference in pathogenesis. Autoimmune reactions are more common in women and circulating non-organ-specific antibodies are found more often in women patients with alcoholic liver disease than in comparable men.<sup>4</sup> Smooth muscle antibodies were detected in 45.4% of women and only 23.4% of men ( $p < 0.05$ ). Similarly, antinuclear antibodies were more prevalent in women and their mean serum IgG and IgM concentrations were higher.<sup>4</sup> Lymphocyte cytotoxicity towards isolated hepatocytes has also been shown in patients with alcoholic hepatitis,<sup>35</sup> but as yet there are inadequate data on the relative frequency of cytotoxic reactions in men and women. Because of their greater propensity for autoimmune reactions, female drinkers may be more likely to develop alcoholic hepatitis and by so doing progress to cirrhosis more rapidly than men.

There is no convincing evidence that the rate or pathways of alcohol metabolism differ in the two sexes or that there are sex-related differences in the major alcohol-metabolising enzyme, alcohol dehydrogenase.<sup>36-39</sup> Differences in body composition between men and women do, however, influence the physiological effects of alcohol. Alcohol has a smaller volume of distribution in women because adipose tissue, into which it diffuses slowly because of the poor blood supply, forms a greater proportion of the body mass (33%) in women than in men (21%).<sup>23</sup> Hence, even if the dose is adjusted for body weight, administration of alcohol will result in higher systemic blood concentrations in women than in men<sup>38-40-41</sup> and might reasonably be expected to cause more liver damage.

### Implications for clinical practice and prevention

The finding that women develop alcohol-induced liver damage more readily than men is of more than academic interest for it implies that treatment facilities and screening

programmes must be designed specifically for them if the problem is to be contained. Since women present with more advanced liver disease than men it is particularly important that they abstain from alcohol. Many female patients have husbands who are also heavy drinkers, so family therapy may be particularly valuable<sup>42</sup>; newer psychological techniques such as assertive training and treatment of co-existing depression can help the individual patient.

Screening women for alcoholic liver disease has been neglected in the past with most surveys and employment-based screening programmes concentrating on men; women employees must now be included. Doctors must also be aware of the possibility of alcoholic liver damage in women presenting with non-specific abdominal symptoms and make greater use of mean cell volume (MCV) and serum  $\gamma$ -glutamyltransferase activity as possible indicators of a high alcohol intake.<sup>43 44</sup>

Emphasis on earlier diagnosis must be accompanied by educational programmes to increase public awareness of hazardous drinking levels. Women should be advised not to exceed 40 g alcohol (two and a half pints of beer or four single spirits) a day on a regular basis, and men should keep below 80 g.

The sudden increase in alcoholic liver disease among women in recent years also raises the broader issues of the role of the advertising of alcohol and the availability of alcoholic drinks in supermarkets. Advertising of many alcoholic drinks, notably spirits, has been aimed particularly at women,<sup>9</sup> and as an increasing number of women are financially independent and tending to adopt male drinking habits it is hardly surprising that a greater number are drinking excessively.

It is therefore becoming increasingly important for women to learn of the hazardous intake levels to counter this trend, and only then will there be much hope of a fall in the number suffering from alcoholic liver disease.

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### Should a patient having a vegan diet take vitamin supplements?

A vegan diet provides ample amounts of all the vitamins except vitamin B<sub>12</sub>, which is found in appreciable amounts only in foods of animal origin. Most vegans are well informed about nutrition, and many provide themselves and their children with one of several proprietary vegetarian food preparations fortified with vitamin B<sub>12</sub>.<sup>1</sup> If one of these is not taken regularly a supplement of the vitamin is indicated.

<sup>1</sup> Purves R, Saunders TAB. An assessment of the nutritional status of preschool vegan children. *Proceedings of the Nutrition Society* 1980;**39**:79A.