Analysis of liver disease in europe

To what extent does alcohol contribute to liver disease in Europe?

Alcoholic liver disease is the major complication of chronic alcohol abuse, with cirrhosis (with or without portal hypertension), being the most common end-point of the spectrum of complications. This association is seen throughout virtually all populations, demographic groups and clinical sub-sets. (Walsh K et al. 2000)

It is notable that the incidence of the disease process is changing on a world-wide consideration, with countries such as India and Japan recently seeing a rapid escalation in numbers of cases of cirrhosis, from their traditionally low baseline of prevalence of the disease. This essay however, will primarily consider the situation in Europe.

Considerations of safe limits to alcohol consumption have to be prefaced with the comments that they are controversial, and that there is no common agreement on a minimum safe level. In the UK, the Royal College of Physicians suggest a weekly limit of 21 units (210 g) of alcohol in men and 14 units in women as being the upper limit of " safe" use. This has to be seen in the context that the Office of Population Censuses and Surveys' General Household Survey found that 27% of men and 13% of women in the UK were found to be exceeding these limits in 2004 (OPCS 2004)

This can be contrasted with the findings of an Italian study (Bellentani S et al. 1997) which suggested that the " significant risk threshold" for the subsequent development of alcoholic liver disease in an Italian population was only 30g of ethanol per day and that the risk escalated with progressively higher levels of intake. The authors also noted that, for a given

level of intake, women had a significantly higher risk of developing alcoholic liver disease than did age-matched men. On a critical note, one must concede that this was a prospective non-randomised study with a moderate (6, 500) entry cohort. This can be compared with a larger Danish study (13, 000 entry cohort) which demonstrated a statistically significant increase in the risk of alcoholic liver disease at levels of intake above 14 – 27 units per week in males and 7 – 13 units in females. (Becker U et al. 1996)

One cannot conclude, from this data, that different European populations have different susceptibility to alcoholic liver disease. One of the major practical difficulties in mounting a major prospective study of this nature is the control of the huge number of variables that may influence the outcome, not least of which is the fact that no individual person drinks a uniform quantity of alcohol per day over many years. There are also considerations of the possibility of variation of effect of different proprietary brands of alcohol-containing drinks as well as the (largely under researched) area of the long term effect of binge drinking.

Virtually all studies however, demonstrate a steep dose dependent increase in alcoholic liver disease above a threshold level of alcohol intake with women having a greater incidence of the disease than men at a given age range and level of intake.

The reasons for this sex difference is not completely clear with Kwo et al. demonstrating that if one adjusts for body mass and liver size, then both men and women have equivalent biological rates of alcohol degradation. (Kwo P Y et al. 1998)

A number of authorities (viz. Teli M R et al. 2005) suggest that these gender differences in susceptibility to alcoholic liver disease may be due to primarily to pharmacokinetic reasons including differences in the rates of ethanol absorption or alternatively, differences in the degree of response of the liver to alcohol induced injury such as that caused by oxidative by-products of ethanol metabolism in the liver.

If one accepts the difficulties inherent in trying to define the lower margins of " safe" levels of alcohol drinking, then it is also appropriate to consider the problem from the other end of the spectrum. There are many studies in the literature which have considered the incidence and natural history of alcoholic liver disease in a population of heavy drinkers who, by definition, will show a much higher prevalence of the disease process.

A comparatively old study by La Vecchia et al. showed a Europe-wide reducing trend in alcoholic liver disease in the recent past (La Vecchia, C et al. 1994) and this should be compared with data which shows that the deaths from alcoholic liver disease are actually increasing in the UK (CMO 2001). More specific recent data shows that this increase is disproportionately represented by the young adult and middle aged population in the UK showing an 8-fold rise since the 1970s (Leon, D. A et al. 2006)

There is a general perception that end-stage alcoholic liver disease (in the form of cirrhosis) is only seen in those patients who demonstrate alcohol dependence syndrome (viz. Smith et al. 2004 and Luca A et al. 2007). There

is a growing body of evidence which suggests that this may not actually be the case.

If one considers one of the landmark papers on alcohol dependence and related disease processes, one could cite the classification of Jellinek who categorised five " sub-species" of alcoholism in his authoritative work in the area. (Jellinek, E. M. 1960 A). The current significance of his initial classification is that he identified two specific types of " alcoholics", the ' ß alcoholics' who are not alcohol dependant, but who have a disproportionately high incidence of alcohol-related diseases, such as cirrhosis and contrasted this to the gamma alcoholics who were typically highly physically dependent, demonstrated frequent behavioural problems and had a high incidence of sociological complications.

Jellinek made deductions about why these groups had different drinking patterns suggesting that the tendency towards heavy drinking in the ß alcoholic group was related to the customs and peer pressures within their social group, whereas gamma alcoholism was characterised, in part, by drinking to relieve a psychological craving and a physical addiction. (Jellinek, E. M. 1960 B). In the context of this examination, one can intuitively suggest that the customs, peer pressures and social groupings may be one of the more salient causes of different patterns of alcohol use across the various national cultures of Europe.

There is a further difficulty in that, a brief overview of the literature on the subject of alcoholic liver disease shows that, in the context of Jellinek's theoretical framework, which describes the population of drinkers who

present to healthcare professionals with liver disease as a distinctly separate (although overlapping) population from those who present with alcohol dependence, there is a comparative paucity of studies which look at the drinking patterns, social factors and attitudes in patients with alcoholic liver disease when one compares it with the wealth of literature on alcohol dependence. This may seem to be an academic inference, but one can cite the authority of the often quoted Wodak study which identified significant differences between the population of typical patients with alcoholic liver disease and a population of patients who were recruited from an alcohol treatment centre for dependence, presenting evidence that only 18% of patients who had clinical alcoholic liver disease were severely dependent on alcohol and this contrasted with 56% of the attendees at the alcohol treatment centres. The authors also found that 63% of the patients who were found to have alcoholic liver disease had only a mild or moderate dependence on alcohol. (Wodak, A. D. et al. 1983). If one looks beyond the confines of Europe, one can cite the authority of an Indian study (Sarin, S. K et al. 1998) which found broadly similar results.

More recent studies using liver transplant patients (viz. Burra, P. et al. 2000) have also produced similar results, although there is an obvious source of potential selection bias in such studies in the desire of certain patients to be accepted onto a transplant programme and this bias will (intuitively) vary between the different patterns of medical care provided across Europe.

The problem confronting many researchers is the difficulty in clinically defining alcoholic liver disease. Many patients may be unaware that they are developing significant problems until the time of presentation. The first

presentation may be with acute upper gastrointestinal tract haemorrhage or with alcoholic hepatitis. Both conditions frequently present in the absence of warning signs of a developing alcohol dependence. (Vorobioff J et al. 1996). The Harry et al. study reporting that the first presentation of alcoholic liver disease may actually be fatal with uncontrollable bleeding oesophageal varices carrying an immediate 25% mortality rate, (Harry, R. et al. 2002), a finding also found in the Brett study. (Brett, B. T. et al. 2001).

Mathurin suggests that in patients who present with severe alcoholic hepatitis, over 50% may die. (Mathurin, P et al. 1996)

If one considers data from other European centres, the Italian Loguercio study considered the pattern of drinking in indigenous Italians who had Hepatitis C. (Loguercio C et al. 2000). This is particularly significant in the Italian population as their prevalence of Hepatitis C is the highest in Europe. (De Bac, C. et al. 2004). It is well known that Hepatitis C infection is associated with a higher incidence of hepatocellular carcinoma, but it is not know the extent to which subsequent alcohol intake influences the natural progression of the disease process. The Loguercio study sought to explore this feature and makes the observation that only 4 – 5% of all manuscripts submitted to " Hepatology" deal with alcohol-related liver disease, which exemplifies the point made earlier.

In direct consideration of the thrust of this examination, the extent to which alcohol contributes to liver disease is modified by the presence of complicating factors such as Hepatitis B and C. Loguercio et al. suggest that there is a direct interaction between alcohol and the viruses, other

authorities (viz. Ostapowicz, G et al. 1998) suggest that an additional mechanism of disease modification is that the presence of alcohol affects the response to interferon therapy (IFN). The latter belief has a poor evidence base as Mabee points to the fact that, without exception, none of the controlled trials published thus far on the efficacy of IFN treatment of Hepatitis C-related liver disease have determined the alcohol intake levels prior to therapy. ((Mabee, C. L. et al. 2008)

Lieberman has shown that chronic alcohol intake levels correlate well with gamma-glutamyl transpeptidase (GT) levels. (Lieberman, M. W. et al. 1995) and these levels have been shown by Camps to be extremely predictive of treatment (Camps, J. et al. 1993). In this way it is possible to make the direct connection that alcohol intake clearly directly influences the rate of progression of hepatic pathology, a claim that has been further strengthened by the large retrospective analysis by Pol et al. who examined and correlated the rate of progression of the disease process (in Hepatitis C and HIV/AIDS hepatitis, with the overall intake of alcohol. (Pol, S. et al. 1998). The authors demonstrated that alcohol intake of the patient directly influences their gamma-glutamyl transpeptidase (GT) plasma levels and the rate of progression of the disease process.

There is further evidence of the degree to which alcohol influences liver disease, at a histological level, in the form of the Scheuer paper. (Scheuer, P. J. et al. 2001). In congruence with the thrust of this segment of the paper, we can cite the authority of Scheuer who correlated the degree of fibrosis and steatosis with the average levels of alcohol intake and Pessione who noted

that the degree of fibrosis in patients with Hepatitis C chronic hepatitis was related to the history of alcohol intake. (Pessione, F. et al. 1998)

To return to the Loguercio study, the authors comment that the Italian cohort was typical for the country, (but atypical for Europe) as there is known to be a high alcohol intake per head of the population in Italy, even after making allowances for the fact that alcohol intake has fallen in the last decade (SPE 2004). In an attempt to evaluate the effects of alcohol on the population with alcoholic liver disease the study considered three important markers namely :

(1) To estimate how many subjects in our country misused alcohol before and after being diagnosed as having HCV-related chronic liver disease

(2) To determine if their drinking habits affected the principal aspects of this disease: routine laboratory data (particularly GT plasma levels), histological pattern (particularly liver steatosis and fibrosis), HCV RNA levels, and response to IFN therapy;

(3) To compare results from this and a previous study (Aricò et al., 1994) to determine if CLD subjectshave modified their drinking habits since a decrease was observed in the general population.

(Loguercio C et al. 2000).

The study is both long and complex, with rigorous statistical analysis. In essence, the authors were able to demonstrate that the majority of patients with Hepatitis C liver disease still regularly drank significant amounts of alcohol. Patients with hepatitis were more likely to drink alcohol than those

with cirrhosis. They were also able to confirm that there were significantly higher levels of gamma-glutamyl transpeptidase (GT) and greater levels of fibrosis associated with higher levels of alcohol in male subjects. Interestingly, women had higher levels of fibrosis than men even if they were total abstainers or less than 40 g/daily of alcohol, but their gamma-glutamyl transpeptidase (GT) levels did reflect the overall alcohol intake. This is very supportive of the hypothesis that women appear to have lower levels of defence against the oxidative insult produced by alcohol intake and may therefore develop a more marked fibrotic infiltration. We know, from other evidence that clinically, women appear to have more severe and rapidly progressive hepatitic disease processes than men. (Watson, R. R. ed. 2001)

To consider a more general overview of the Europe-wide situation, one can consider the Rehm review paper which considers the implications of alcohol usage and mortality rates across the European continent. (Rehm J et al. 2007). The review itself is in commendable depth and provides an excellent evidence base for the area of investigation. The main points presented can be summarised. There is still a general all-cause mortality gradient from west to east across Europe which is more pronounced in males. (Zatonski W et al. 2000). In statistical terms, the western (old EU) countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden and UK) had a male life expectancy of 75. 7 yrs and a female life expectancy of 81. 5 yrs. In the central European countries (Czech Republic, Hungary, Poland, Slovakia, and Slovenia) these expectancy figures have fallen to 70. 9 and 78. 7 respectively. In the new Baltic states (Estonia, Latvia, and Lithuania) it is 65.

3 and 76. 8 yrs respectively and in the Russian Federation it was 58. 3 for men and 71. 8 for women. It can be seen from these figures that the life expectancy for men varies by 17. 4 years and 9. 7 yrs for women. It should be noted that a later, but less exhaustive, study by Vagero demonstrated that by 2005, while life expectancies were slightly higher, the overall gradient and pattern of mortality remained unchanged. (Vagero D 2007). A number of authorities (viz. Men T et al. 2003 and McKee M et al. 2001) have highlighted the levels of alcohol consumption, in addition to smoking and poor nutrition, as being the main determinants of this gradient. Rhem has also identified alcohol as being the prime determinant of premature mortality in the Russian federation. (Rehm J et al. 2003 A)

Rhem presents a systematic analysis of alcohol-attributable mortality and disease burden by country, and considers two major aspects in each case namely, both the level of consumption and the patterns of drinking, the latter mainly referring to irregular heavy drinking occasions. (Rehm J et al. 2007).

These two aspects are not straightforward, as an illustrative example of France and Sweden demonstrates. France has a traditional wine drinking culture with overall high levels of alcohol consumption but a relatively low proportion of people drinking to intoxication, Sweden, by contrast, has an increasing, but still relatively low level of overall alcohol consumption but a social tradition of irregular heavy drinking.

The study highlights Hungary as being notable for having the highest mortality rates in the EU for several alcohol-related pathologies such as liver cirrhosis, together with malignant neoplasms of lip, oral cavity and pharynx.

It is reported that for the age range 20 – 64 yrs, alcohol plays a part in premature deaths of 25% of the population of Hungary. Cirrhosis is particularly high in Hungary and it is postulated that the high consumption of home made spirits may be a relevant factor. (Szucs S et al. 2005). It is also recognised that the culturally acceptable pattern of drinking in Hungary to a high level of alcohol intake with many heavy drinking occasions.

The study gives a graphic breakdown of alcohol-related indices across the continent thus:

	New EU member states				Old EU member states		
	Czech Republic	Hungary	Lithuania	Poland	France	Sweden	UK
Adult per capita in l pure alcohol	17. 0	14. 9	17. 2	11. 7	14. 5	9. 9	13 4
Recorded in l pure alcohol	16. 0	11. 9	12. 3	8. 7	13. 5	6. 9	11 4

Unrecorded in l pure alcohol	1. 0	3. 0	4. 9	3. 0	1. 0	3. 0	2.
Patterns of drinking [a]	2	3	3	3	1	3	3
Preferred beverage	beer	wine/ beer/ spirits	beer/ spirits	spirits/ beer	wine	beer	be r
Men							
% abstention/very light drinking	9. 0	12. 0	10. 0	16. 4	7. 3	10. 0	9.
% > 40 g/day [b]	59. 4	47. 0	41. 0	38. 5	50. 8	18. 3	38 6
Women							
% abstention/very light drinking	19. 1	27. 0	28. 0	34. 3	11. 1	16. 0	14 3
% > 40 g/day	7. 0	16. 0	8. 0	9. 0	7. 0	3. 8	10 3

[a] Estimated average pattern of drinking (1–4 with 4 being the most

detrimental pattern; see text for more explanation and [13] for the full algorithm used).

[b] > 40 g/day on average correspond to more than 3–4 drinks on average per day (1 drink is one can of beers of 0. 33 l or one small glass of wine or one shot of spirits).

(After Rehm J et al. 2007).

There is considerable discussion surrounding the issue of alcohol-attributable mortality and death rates in the various European regions with Russia yielding the highest figures (29. 0/10, 000 person-years). An unexplained anomaly was found in that France and the UK show consistently higher rates of alcohol-attributable mortality in women than the general trend in the other countries when compared to the equivalent male rates. The overall alcohol-attributable mortality is greater in the male population with the ratio difference being much greater in the new EU member states, where the culture dictates that a smaller proportion of the alcohol produced is consumed by women

Alcohol has been defined as only one of the causes of premature mortality (see above). Rehm suggests that alcohol is the major factor as, if the alcohol-related mortality is removed and the mortality figures adjusted, then the premature mortality rates between the highest and lowest rated countries become much more similar.

Premature alcohol-attributable deaths in eight European countries by sex and age groups as proportions (in %) of all deaths, for the year 2002

Age group	New EU member states				Old EU member states		
	Czech Republic	Hungary	Lithuania	Poland	France	Sweden	UK
Men							
20–44	28. 5	39. 4	38. 4	26. 0	22. 9	19. 2	22. 2
45–64	14. 0	22. 2	16. 4	10. 2	16. 6	7. 1	7. 6
20–64	16. 3	25. 2	22. 8	13. 6	18. 0	9. 3	10. 7
Women							
20–44	14. 2	19. 5	21. 4	10. 7	10. 9	6. 9	12. 5
45–64	4. 5	12. 7	10. 1	2. 1	9. 6	2. 2	4. 6
20–64	5. 8	13. 7	12. 4	3. 6	9. 9	2. 9	6. 0

The estimates for Russia are underestimates, as several disease categories could not be included because of the different classification system of diseases

(After Rehm J et al. 2007).

It has to be acknowledged that with all of the papers cited in this examination, there are a number of potential shortcomings as data from different countries is inevitably subject to different categorisations and different modes of collection. Equally, differential rates of confounding factors such as Hepatitis C, HIV/AIDS, smoking and nutritional differences, all of which impact on the clinical presentation of the alcoholic liver disease process are difficult to completely isolate and account for. An additional complicating factor is that it has long been recognised that small amounts of alcohol have a cardio protective effect

(Rehm J et al. 2003 B), irregular heavy drinking occasions (binge drinking) adding up to the same average volume of drinking over a period of time are associated with increased risk of vascular events. This increased risk is hard to separate from the increased risk of mortality from alcoholic liver disease. This is particularly the case with the Russian experience where drinking typically follows irregular heavy drinking patterns and the cardioprotective effect is probably negligible on a population-wide assessment. (Nicholson A et al. 2005)

In overview, one can conclude that alcohol plays a substantial, and geographically variable role in premature adult mortality across Europe with 15% of all deaths in the 20 – 64 yr age range being attributable to this risk with men comprising a higher proportion than women in this total. (Rehm J et al. 2006).

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