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Liver disease in the elderly

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Ageing of the liver mainly affects the sinusoids and the Kupffer cells. Pseudocapillarization, manifested by reduced sinusoidal fenestration and subendothelial collagen deposition, causes a reduction in oxygen-dependent hepatocyte functions such as oxidative drug metabolism. The liver mass in old people is somewhat reduced and the liver blood flow is diminished. This causes a reduction in the clearance of rapidly cleared drugs, but the clearance of slowly cleared drugs is not affected. The overall capacity of the liver to regenerate is maintained in old people. Therefore, hepatic resections for hepatocellular carcinoma can be carried out in non-cirrhotic elderly people. For liver transplantations, biological age is more important than calendar age. Transplantations in frail old people and in elderly people with very poor liver function are associated with increased morbidity and limited survival. In relatively healthy old people, the results are as good as those in younger age groups. An increased prevalence of hepatitis C associated cirrhosis and hepatocellular carcinoma in the elderly population is to be expected, at least in the next 20 years. There is a high prevalence of gallstones among old people, in particular among females. For symptomatic choledocholithiasis in elderly patients, endoscopic bile duct clearance does not necessarily need to be followed by cholecystectomy.

Key words: liver function; elderly; old age; non-alcoholic steatohepatitis; viral hepatitis; hepatocellular carcinoma; alcoholic liver disease; cholestatic liver disease; liver transplantation; gallstones.

Compared to the musculoskeletal and cardiovascular systems, the liver is less affected by ageing. The peak incidence of most liver diseases is in the third and fourth decades. Moreover, old age is not associated with any liver disease in particular. However, as the mean age of populations in Western societies has increased, the number of old people with liver disease has also risen. In this chapter, we will discuss a number of issues that need special attention when they occur in elderly people with liver disease.

LIVER FUNCTION AND OLD AGE

Ageing is associated with a decrease in liver mass and hepatic blood flow.[1–3] In elderly men, liver weight is reduced by about 6.5% and in women by 14.3%.[4] These changes are not dramatic, but a decrease in hepatic blood flow reduces the metabolism of rapidly cleared drugs such as propranolol, amitryptiline, verapamil and morphine.[5] Also, the clearance of theophylline is decreased, especially in non-smoking elderly persons.[5] In isolated hepatocytes from the livers of young and old people and rats, phase I oxidative

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metabolism and phase II conjugation reactions occur at similar rates.[6,7] However, in vivo rates of oxidative phase I drug metabolism in old rats was impaired, while phase II glucuronidation was preserved.[5] This difference between in vitro and in vivo oxidative metabolism has been attributed to a diffusional barrier with decreased oxygen delivery in the livers of old animals. Pseudocapillarization of the hepatic sinusoids in aged rat livers may be the anatomical basis for this reduced oxygen delivery. This results in a decrease in the number of fenestrae, thickening of the sinusoidal endothelium and some deposition of type IV collagen in the space of Disse. Pseudocapillarization differs from the capillarization that occurs in cirrhosis, where it is associated with the appearance of complete basal lamina (normally absent in sinusoids), loss of hepatocyte microvilli, fibrosis and nodular regeneration. As a consequence of pseudocapillarization, hepatocytes in the livers of old rats suffer from a degree of hypoxia. ATP/ADP ratios are, therefore, significantly lower in old compared to young rats.[8] These changes could be of importance for drug therapy in old age. In particular, the clearance of drugs undergoing oxidative metabolism, such as propranolol and theophylline, is impaired.

Impairment of Kupffer cell function may be another factor affecting elderly people.[9–10] Kupffer cells are macrophages with a major function in the removal of endotoxins. Impairment of Kupffer cell function may play a role in the increased susceptibility of old people to sepsis secondary to abdominal infections. Kupffer cells also limit the hepatic spread of metastases. In experimental animal models, depletion of Kupffer cells prior to injecting adenocarcinoma cells led to a massive implantation of carcinoma cells in the liver, much more so than in livers with intact Kupffer cell function.[11,12] Therefore, impaired Kupffer cell function may have consequences for metastatic liver disease in the elderly.

After toxic injury, the liver of old rats regenerates more slowly than the liver of young rats, whereas the overall regeneration capacity is preserved.[13,14] Hepatic resection for hepatocellular carcinoma can, therefore, be done safely in elderly patients without cirrhosis (see below).

In extrapolating animal studies to humans, one has to differentiate the frail from the healthy elderly. For instance, clearance of metoclopramide was reduced in frail but not in healthy subjects older than 65 years.[15] Liver volume in this study, as measured by ultrasonography, was no different between old and young subjects. In another study, liver volume was lower in older subjects. However, paracetamol conjugation was only impaired in frail but not in healthy elderly subjects.[16] Zoli et al[2] reported that total hepatic blood flow, as measured by echo-Doppler, as well as the functional hepatic blood flow, as measured by sorbitol clearance, decreased with age in human subjects. Williams and Woodhouse[6] showed that in human liver biopsies, aldrin epoxidation and 7-ethoxy-coumarin-O-de-ethylation was unimpaired in old people. This suggests that impaired oxidative drug metabolism in old people is not due to a decreased intrinsic capacity of the microsomal mono-oxygenase system but, rather, is due to impaired blood flow and/or an increase in the oxygen diffusional barrier as described for rats (Table 1).

There is an increased incidence of adverse drug reactions among the elderly population. However, this cannot be ascribed to reduced drug metabolism but, rather, to the fact that older patients are exposed to more drugs at the same time.[17]

HEPATITIS C

Hepatitis C is currently the most prevalent viral liver disease in Western societies. The peak incidence of hepatitis c virus (HCV) infections occurred in the 1970s before

Table 1. Functions of the ageing liver.

Liver function	Affected by age
Liver mass	+
Portal blood flow	+
Fenestration of sinusoids	+
Kupffer cell function	+
Rate of liver regeneration	+
Regenerating capacity	−
In vitro oxidative drug metabolism	−
In vivo and in vitro glucuronidation	−
In vivo clearance of rapidly cleared drugs	+
In vivo clearance of slowly cleared drugs	−
Alcohol dehydrogenase	−

reliable tests for HCV detection were available. The progression of the disease is slow. The reported lag time between infection and the development of chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC) is 10, 20 and 30 years, respectively.[18] When contracted at an older age, HCV disease progression is more rapid. The recent prevalence of anti-HCV antibodies among residents of an American nursing home was about 4.5 times that in the general population.[19] During the next 20 years, the prevalence of HCV-related cirrhosis and HCC among elderly people is expected to rise even further.[20] Widespread early combination therapy with interferon and ribavirin may reverse this trend.[21] For the elderly, it is of particular importance that the rate of progression to cirrhosis is retarded by therapy.[22]

HEPATITIS B

Among elderly people of Asian origin, the prevalence of hepatitis B is still high. In Western societies the prevalence of hepatitis B among elderly people is low. For example, the prevalence of HbsAg in an American nursing home was 0%, while in a Japanese nursing home it was 5%.[19,23] Hepatitis B in elderly patients can present as chronic hepatitis, but more often as cirrhosis. HCC in elderly patients of Asian origin will mostly be hepatitis B virus (HBV)-related. Unlike hepatitis C, HBV-related cirrhosis is a contra-indication to interferon therapy. Interferon therapy often leads to a temporary but sometimes considerable flare-up of inflammatory activity. This may push a cirrhotic liver from a compensated into a decompensated stage. Lamivudine may be an alternative for the elderly patient with Child A cirrhosis, but the results of trials are still awaited.

ACUTE VIRAL HEPATITIS

Acute viral hepatitis is becoming more important in the elderly. Currently, anti-hepatitis A virus (HAV) antibody prevalence among old people is still high, as a recent study from Belgium showed. Prevalence of anti-HAV among 0–14-year-old Belgians was 5.4% but increased to 31.7%, 60.8% and 80% in the 25–34, 35–44 and $>$55-year-old age groups, respectively.[24] In an American nursing home the prevalence was 80%.[19] In the future, the anti-HAV immune status of elderly persons may decrease. Increased mobility of elderly

persons, including travel to endemic areas, leads to increased exposure to hepatitis A and E. In general, acute hepatitis A has a good prognosis, with a case fatality rate of 0.3%. However, the case fatality rate increases above the age of 40.[25] For comparison, the case fatality rate of hepatitis B and non A-non B hepatitis is 1.0–1.2% and 1.5–2.5%, respectively.[26] Vaccination against HAV infection is recommended for senior travellers visiting developing countries. In the group aged >35 years, pre-vaccination antibody testing is recommended.[24] Acute hepatitis A in patients with chronic hepatitis or cirrhosis of viral or non-viral origin carries a high mortality risk. Therefore, vaccination against hepatitis A should be considered in elderly persons with chronic liver disease.

ALCOHOLIC LIVER DISEASE

The prevalence of alcohol abuse among the elderly is probably underestimated.[27] A study from Germany showed that 7.4% of nursing home residents have alcohol problems.[28] Risk factors for alcoholic liver disease are obesity and underlying liver disease, in particular haemochromatosis and hepatitis C. Age per se has no effect on the activity of alcohol dehydrogenase in the human liver.[29] Genetic factors play a role in the establishment of chronic alcoholic liver disease,[30] perhaps explaining why only 10% of alcohol abusers will get liver disease. In the elderly population, heavy social drinking is probably more of a problem than real alcoholism. Heavy alcohol use and hepatitis C is an unfavourable combination. In several studies, mortality from liver-related causes in hepatitis C infected patients was, in fact, due to a combination of hepatitis C virus infection and chronic alcoholism.[31,32]

NON-ALCOHOLIC STEATOHEPATITIS

After viral and alcoholic liver disease, NASH (non-alcoholic steatohepatitis or non-alcoholic fatty liver disease), is, in practice, the third commonest liver disease. It is associated with insulin-resistance, diabetes mellitus and obesity, in particular abdominal adiposity. Complaints include right upper quadrant pain, fatigue and malaise. The presenting age is between 46 and 57 years. NASH is thus seen in elderly patients. Since oxidative stress, lipid peroxidation, endotoxin and tumour necrosis factor-α (TNFα) may be aetiological factors, therapies with anti-oxidants and non-absorbable antibiotics have been tried. Since ethanol induces CYP2E1, an enzyme of the cytochrome P450 family that is thought to play a role in the pathogenesis of NASH, absolute alcohol restriction is recommended.[33–35] A pilot study on the effect of ursodeoxycholic acid and clofibrate on NASH showed a beneficial effect for ursodeoxycholic acid but not for clofibrate.[36] In obese mice, metformin has been shown to be effective. However, the efficacy of this drug has not been proved yet in humans for this indication. Moreover, metformin has the potential to cause lactic acidosis in patients with liver disease.[37] Therefore, the drug should be used with caution, if at all. Gradual, not abrupt, weight loss is recommended. Sudden weight loss may cause an increase in inflammation. This is probably due to an influx of fatty acids from abdominal adipose tissue.[38]

CHOLESTATIC LIVER DISEASE

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are chronic diseases that can present in adult patients of any age. In a cohort of more than

1000 patients in the area of Newcastle upon Tyne, UK, 39% of patients with PBC presented at an age of over 65 years. Symptoms on presentation were no different in old and young age groups. Liver-related deaths were more common in the old age group (18% versus 13% in the groups aged over and under 65, respectively).[39]

Of patients with PSC, 70% have inflammatory bowel disease (IBD). The symptoms of IBD often precede those of liver disease. Presenting symptoms of PSC in older persons are probably no different to those in younger patients, with perhaps slightly more cholangiocarcinoma on presentation in the older age group. Cholangitis and obstructive jaundice in these patients can be handled endoscopically.[40] Whether endoscopic dilatation of dominant bile duct strictures will postpone cirrhosis or affect mortality is not yet known. Eventually, most patients with PSC will need a liver transplant. It is probably wise not to wait for liver transplantation until a person is aged over 60. Most patients with PSC are transplanted before they reach that age.

HEPATOCELLULAR CARCINOMA

Recently, an increased incidence of hepatocellular carcinoma (HCC) has been observed, both in the USA and in Europe. This is mostly due to a rise in HCV-related HCC. The incidence of HBV- and alcohol-related HCC has remained stable.[41] The overall increased life expectancy has resulted in an increased number of elderly people with HCC. However, the absolute rise in the incidence of HCC must be attributed to an increase of HCV-related HCC among younger people.[42]

Short-term survival rates for HCC patients used to be higher among younger patients, but more recent data show that these curves have a tendency to merge. For example, 1-year survival of 40–59 year old patients increased from 14.3% in 1977–1981 to 24.8% in 1992–1996, while 1-year survival of patients older than 60 years increased from 10.8% to 20.9% in the same period.[43] However, 5-year survival continues to be low (for 40–59 year old patients it is 7%; for those older than 60 it is 4.5%).[43]

Early diagnosis of HCC remains a clue to the management of this disease. Ultrasound, computed tomography (CT) scanning using intravenous contrast enhancement, magnetic resonance imaging (MRI), α-foetoprotein and des-gamma-carboxy-prothrombin measurements contribute to the early detection of HCC. The efficacy of early detection will be higher among patients already under surveillance for chronic liver disease. There is no proof that population screening is cost-effective.

Radiofrequency ablation, alcohol injection and transcatheter arterial chemoembolization are non-surgical treatment modalities for HCC.[44,45] In general, non-surgical treatments are not curative.[46] Only transplantation and resection offer hope for cure. Resection should be restricted to patients without cirrhosis, or with only Child–Pugh class A cirrhosis without portal hypertension. In Western countries this represents less than 5% of patients.[47] Tumour recurrence after resection remains high (50% after 3 years).[48] A recent study showed no difference in survival after hepatic resection for HCC between patients younger and older than 70. Also, post-operative complications were no different in the two groups.[49] However, resection of HCC in patients >70 years with cirrhosis has a less favourable prognosis with regard to disease-free survival.[50]

Transplantation is carried out for single tumours $\leqslant 5$ cm in diameter or for up to three tumours of $\leqslant 2$ cm diameter each.[51] However, on an intention-to-treat basis the results of this approach are deteriorating due to long waiting times and mortality while on the waiting list.[52] When waiting time exceeds 6 months, as is the case now in most centres, there will be an exceedingly high pre-operative dropout rate. Whether

chemo-embolization or resection prior to transplantation can remedy this needs to be investigated.[53,54]

LIVER TRANSPLANTATION

Liver transplantation has become the routine treatment for patients with fulminant hepatic failure, chronic decompensated liver disease and hepatocellular carcinoma of limited size (see above). There is no real age limit for liver transplantation, but biological age is an important determinant of patient survival. In a recent study, 600 patients younger than 60 years were compared with 135 patients older than 60.[55] About 20% of these patients had chronic viral hepatitis and 40% had PBC, PSC or alcoholic liver disease. Several post-transplant variables were compared. Time in intensive care units (ICUs) and post-operative hospital stay were longer in the older age group. This was mainly due to a small subgroup with prolonged ICU and hospital stay. Median ICU and hospital stay was no different (3 and 15 days, respectively). Quality of life 1-year after transplantation was slightly better in the older age group. The proportion of older recipients surviving 1-year after liver transplantation was 81% versus 90% in the younger group. This difference is statistically significant. Long term data show that the survival curves become more disparate at 5 years after transplantation. Five-year survival was 52% in patients older than 60, and 75% in younger patients.[56] The recipient's age was particularly important as a predictive factor for survival among patients with hepatitis C.[55] Graft survival in younger and older patients was the same.[55] Not all studies have agreed on this: in another study, 1-year graft survival was 70% for patients older than 60 years and 80% for patients younger than 60.[57] Excess mortality one year after transplantation in the older age group was mainly due to infections, cardiac and neurological causes (stroke, intra-cerebral haemorrhage).[55] Five years after transplantation, elderly patients more often died from malignancy than did younger patients.[56] A retrospective study of 1446 liver transplant recipients, including 241 patients older than 60 years, revealed that low-risk elderly patients did as well as younger patients. However, elderly patients with poor liver function or a high serum bilirubin concentration had lower survival rates.[58] Thus, with resources for liver transplantation becoming scarcer, one should be cautious in transplanting patients older than 60 years with poor liver function.

GALLSTONES

The incidence of gallstones increases with age. A systematic ultrasound study among the population of the Italian town of Sirmione revealed an overall prevalence of gallstones of 6.7% in men and 14.6% in women. In the higher age group (50–65 years), 27% of females and 11% of males had gallstones.[59] In 78% of cases the gallstones were asymptomatic. Other Italian studies have confirmed these figures.[60] The prevalence of gallstones correlates with age, gender, obesity, hypertriglyceridaemia and the number of pregnancies. Diabetes in women and weight loss in both men and women are additional factors.[60,61]

Most stones in Caucasians are cholesterol stones. This is also the case in the older age group, but elderly persons more often have calcified pigment stones than do younger subjects.[60,61] The aetiology of gallstones in the elderly population is not known. Cholesterol supersaturation, a disturbed balance between pro- and anti-nucleating

factors, and reduced gallbladder emptying are possible factors. A recent study showed no difference in gallbladder emptying in persons above the age of 60 years compared to a younger control group.[62]

Laparoscopic cholecystectomy is the treatment of choice for symptomatic cholecystitis. Choledocholithiasis is treated by endoscopic papillotomy and stone extraction. A study of the long-term outcome of endoscopic treatment without cholecystectomy in elderly patients revealed low recurrence rates for both symptomatic cholecystitis and choledocholithiasis.[63] Therefore, in the elderly patient with choledocholithiasis, endoscopic stone clearance is often sufficient and cholecystectomy is not necessary even in patients with gallbladder stones.

CONCLUSIONS

Demographic trends indicate a considerable growth in Western societies of a relatively healthy elderly population. A growth in the number of elderly persons with chronic

Practice points

- the prevalence of hepatitis C associated cirrhosis and hepatocellular carcinoma among elderly people will continue to rise during the next two decades
- non-alcoholic steatohepatitis should be treated by slow and not rapid weight reduction
- alcohol abuse by elderly persons in nursing homes is underestimated
- choledocholithiasis in elderly people is best treated by endoscopic bile duct clearance and does not necessarily need to be followed by cholecystectomy
- hepatocellular carcinoma in non-cirrhotic patients is best treated by surgical resection
- liver transplantation in elderly patients with reasonable liver function has a good prognosis
- liver transplantation in frail old people, or elderly people with poor liver function, has a dismal prognosis and is best not done
- quality of life should be the guiding principle in any surgical or medical intervention in elderly subjects

Research agenda

- there is a need for outcome and appropriateness research for medical and surgical therapy for liver disease in elderly people
- adverse drug reactions in old people are very common, but epidemiological data on this topic are scarce
- pharmaceutical companies should be more creative in their therapeutic goals: non-alcoholic steatohepatitis is very common and should be high on their research list
- with increasing waiting times for liver transplantation, many patients with hepatocellular carcinoma die on the waiting list. Other therapeutic modalities, such as gene therapy, should be pursued more rigorously

liver disease is inevitable. In particular, the number of elderly people with hepatitis C related cirrhosis, hepatocellular carcinoma and alcoholic cirrhosis is expected to grow. In elderly people, maintenance or restoration of quality of life should be the aim of medical care. It is also obvious that the term 'elderly person' is loosely defined: a 60-year-old person can sometimes be 'older' than a 70-year-old person. Major interventions among frail old people carry a significant morbidity and often are not life-saving. Frailty and biological age, therefore, are better indicators than is calendar age.

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