



Liver Disease in Women: A Focused View on Saudis as a Model for the Arabian Gulf Population

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Abstract

Liver disease is a leading cause for morbidity and mortality among males and females. Due to several sex hormonal differences between females and males, manifestations and outcomes of liver diseases are different between male and females and several previous reports had addressed these differences. Reports on liver disease among Saudis are sporadic mostly addressing one or two forms of liver disease separately with limited attention to the sex difference in liver disease. This paper is addressing common liver disease among Saudis, stressing on the gender difference in liver disease.

Keywords

Liver disease; Hepatitis B; Hepatitis C; Autoimmune hepatitis; Hepatocellular carcinoma; Gender

Introduction

Liver disease of varying etiologies is among the leading causes of morbidity and mortality worldwide. International and national data have shown different presentations, outcomes and treatment responses for different liver diseases between women and men [1-6]. In general, men are more likely to die from complications of liver cirrhosis and hepatocellular carcinoma [1-5]. This finding had been reported by previous studies on the effect of female sex hormones and other biological and physiological differences between the sexes [7,8]. Estrogen, which is a potent antioxidant, likely plays a protective role against certain liver diseases in women such as chronic hepatitis B and chronic hepatitis C. Moreover, estrogen likely delays the progression of liver fibrosis in women by inhibiting interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF α), which are both potent pro-inflammatory cytokines, and suppressing hepatic stellate cells [7-10]. Furthermore, estradiol inhibits the apoptosis of hepatocytes. Other evidence has shown that postmenopausal women with liver disease are at a similar risk of liver fibrosis as men [11,12]. In Saudi Arabia viral hepatitis rank the second most common cause for viral infection according to the last Ministry of health annual report, with an approximate annual rate of 104.6, 78.4 and 13.6 new cases per 100,000 for HBV, HBC and HAV respectively [13-15]. Moreover liver disease related complications are among the common causes for mortality in the country [15,16]. On the other hand, several studies

have shown that a normal level of serum alanine aminotransferase (ALT), a specific marker of liver disease, is significantly higher in men than women in the general population we have shown similar finding among Saudis. This finding requires a different understanding of elevated serum ALT between men and women [17-19].

This article reviews the various aspects of different liver diseases in women compared with those in men, with a focus on the available data on viral hepatitis, NAFLD and Autoimmune hepatitis from Saudi Arabia.

HBV Infection in Saudis

Epidemiology

Like other Asian hepatitis B virus (HBV)-endemic countries [20,21], the transmission of HBV among Saudis is predominantly vertical: from a mother to her child during delivery or as a result of infection during the neonatal period. Men are more commonly infected with HBV than women, This finding are similar across Asian countries and international data [20,21]. Aljarbou had shown a prevalence rate of 2% for men and 0.8 % for women and Male to female ratio of 1.8:1 as sown by Al-Tawfiq et al. [22,23]. Similarly Mimish et al. reported Hepatitis B annual seropositivity incidence rate of 123 and 85.5 in 100,000 for men and women respectively [13]. Saudi Arabia formerly had one of the highest rates of HBV. However, since the implementation of an HBV vaccination program, the prevalence had gradually declined from 6.7% in 1989 to less than 0.16 % among adolescents, [15] in the 2000s. Currently, Saudi Arabia has an intermediate prevalence of HBV 0.15 [23,24].

Clinical aspects of chronic hepatitis B (CHB) among Saudi women

The natural history of CHB infection in Saudi Arabia typically has four stages that that characterize perinatally transmitted CHB: the immune tolerance, immune clearance, non-replicative inactive carrier and reactivation phases 1 [15,25,26]. The majority of HBV-infected Saudi women are asymptomatic during the immune tolerant phase. They are commonly diagnosed during premarital screening, during pregnancy or at a blood donation [15,22,27]. Decompensated cirrhosis and hepatocellular carcinoma complications from CHB infections are less commonly reported in Saudi women than Saudi men [5,28-30]. The rate of clearance of perinatally acquires hepatitis B is higher in women than men [31]. This finding might be the reason for lower number of HBV-infected women than men in adolescence and adult hood. Furthermore, evidence has shown that women are less likely than men to progress to cirrhosis and associated complications [32]. A similar finding was shown in our report of CHB in Saudi Arabia, in which men had a 2.6 times higher chance of cirrhosis compared to women [33].

HBV infected women are the primary transmitters of HBV in endemic areas during birth [21]. Evidence from high endemic regions has shown that the implementation of an HBV vaccination program reduced HBV prevalence over the years. In Saudi Arabia, a neonatal HBV vaccination program was initiated in 1989, and a school children vaccination program was initiated in 1990. One report from our center on the effectiveness of the HBV vaccine and HBs

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Ab levels among medical students observed that females had a higher rate of protection compared to males 62.1% and 58.8% respectively. Al Qahtni et al. showed similar results in their report on medical students and healthcare workers from Najran. These findings might also explain the higher prevalence of HBV infection in men in Saudi Arabia (Table 1) [34,35].

Pregnancy and hepatitis B

The hormonal changes during pregnancy are thought to activate HBV replication and accelerate liver disease progression [36,37].

HBV DNA level was found to increase in pregnant mothers infected with HBV late in the course of pregnancy or early postpartum in both HBeAg-positive and HBeAg-negative infected mothers [38]. Serum ALT was also found to be increase in late pregnancy [38]. No similar data are available from Saudi Arabia, however most of HBV infected mother are HBeAg-negative with low chance for viral transmission compared to HBeAg-positive Pregnancy [15]. Infants of HBV-infected mothers are at risk for acquiring the infection vertically during birth [1,36]. This vertical transmission can be reduced by treating mothers with a high viral load using an antiviral therapy [36]. Caesarean delivery can also reduce the risk of transmission during birth [36,37]. The HBV vaccine and hepatitis B immunoglobulin are the major protective strategies for an infant of an HBV-infected mother. These strategies are the current standard of care for neonates of HBV-infected mothers [36,37,39].

Hepatitis D virus (HDV): Data on HDV infection in Saudi Arabia are limited. They mainly focus on prevalence and not on sex differences [40,41].

Hepatitis C Virus (HCV)

Epidemiology

Together with HBV, HCV infection is the predominant cause of chronic liver disease among Saudis [15,22,23].

Although large prevalence report on HCV infection among Saudis are lacking, HCV transmission in the country is thought to be related to blood transfusion, hemodialysis and IV drug abuse [15].

Compared to HBV infection, HCV infection is less prevalent in Saudi Arabia [15,22,42]. In addition, men tend to have a two to three times higher infection rate than women [15,19,43-45]. The most recent MOH data showed that new cases of HBV infection are about 2.6 times more common compared to new HCV. Total of 1686 new cases of HCV reported in the last MOH report [42]. An estimated incidence rate of 124 cases per 100,000 [23,42]. Madani had shown that significant difference in HCV prevalence between

men and women 0.7 and 0.2 respectively [23]. However Mimish et al. showed that the difference between Saudi males and females was not significant 76.8 and 80.1 respectively [13]. Higher rate of HCV infection in males is thought to be related to higher rate of IV blood abuse in males [15,46]. Genotyping shows that HCV genotype 4 followed by genotype 1 are the most prevalent genotypes. However, no genotype difference was observed between men and women [44,45]. Several international studies have shown that HCV-infected women are more likely to clear the virus spontaneously before and after liver transplantation [47-50]. A similar report from our center by Akbar, showed spontaneous clearance of HCV in three patients, of which all of those were women [51].

Clinical aspects

More than 70% of patients with HCV infection will progress to chronic liver disease with complications [48,49,52,53]. Decompensated cirrhosis in chronic hepatitis C as an indication for liver transplantation in Saudis, has been reported in men more often than Saudi women [54] Similarly, hepatocellular carcinoma is a complication of chronic HCV infection that is two to three times more common in Saudi men than Saudi women [30,44,55].

In terms of hepatitis C response according to previous international data, premenopausal women are more responsive to conventional CHC treatment than men or postmenopausal women [32,56-58]. However, studies from Saudi Arabia on CHC treatment with conventional pegylated interferon alpha and ribavirin did not show a difference between men and women in terms of treatment response [59-61].

Non-alcoholic Fatty Liver Disease (NAFLD)

NAFLD is the hepatic manifestation of metabolic syndrome [63]. It is defined as hepatic fat infiltration in more than 5% of hepatocytes in the absence of excessive alcohol intake (more than 10 g of ethanol daily in women) [37,62]

The normal fat distribution in the body differs between men and women. Women have more subcutaneous fat distribution, whereas men and postmenopausal women tend to have more visceral fat accumulation, which carries a higher risk for NAFLD [63,64]. Moreover, postmenopausal women on oral contraceptives have a 50% reduction in the risk of NAFLD [65]. Additional evidence comes from treating women with breast cancer using an anti-estrogen drug (tamoxifen). This drug had been shown to increase the risk of NAFLD [66,67].

Epidemiology of NAFLD

The data concerning the association between being female and NAFLD are controversial [69]. Some evidence shows that NAFLD

Table 1: Number of patients with different forms of common liver disease among Saudi males and females based on available national data.

Disease	Males	Females	Total or percent	Remarks	Reference
CHB	2178 Saudi+570 non Saudi	1369 Saudi +206 non Saudi	4323	Highest In Jeddah city 901 then Riyadh 569	2014 MOH annual report [14].
Hepatitis B vaccine	61.1%	58.8%	Maintained protection	High risk group	[34]
CHC	660 Saudi and 362 None Saudi	526Saudi and 138 females	1686	Highest in Jeddah city 466 then Riyadh 242	2014 MOH annual report [14]
NAFLD	112 (54.1%)	95 (49.1%)	207	P value non-significant	[74]
AIH	8 (24.3%)	25 (75.7%)	33	All patients had type 1 AIH	[77]
HCC	267 (73.6%)	96 (26.4%)	363	Largest number of HCC reported from Saudi Arabia	[31]
Liver transplantation	292 (59.5%)	199 (40.5%)	491	Living related	[112]

tends to affect twice as many men and postmenopausal women than women below the age of 50 [68-71].

NAFLD in Saudi women

The prevalence of NAFLD among Saudis varied from 16.6%-54% in different studies depending on the radiological method and cut-off values used for diagnosis [72-76]. Different studies showed variable rates for NAFLD among men and women. Akbar et al. studied patients with diabetes from our center and showed that women are more commonly affected than men [73]. On the other hand, in a hospital-based study in Riyadh, Al Hamoudi et al. showed that Saudi men are more likely to have NAFLD than women [72]. More recent reports of NAFLD in the Southeast, Hail and Jazan regions of Saudi Arabia did not show a significant difference in the prevalence of NAFLD between men and women [74-76]. The different rates from different studies might be the result of differences in participant age and the diagnostic methods of NAFLD. For example, the mean participant age of Akbar et al. (54 years old) was older than that of Al Hamoudi et al. (45 years old). This difference was also true for other studies [72-76]. This age difference and the inclusion of different percentages of pre- and postmenopausal women might explain the difference in findings of NAFLD prevalence between women and men in different studies. Similar to viral hepatitis HBV and HC infection NAFLD associated HCC, is more commonly reported in men than women [77]. Data on NAFLD associated HCC from Saudi Arabia are limited because most HCC cases in Saudi Arabia are related to chronic viral hepatitis [31,55].

Autoimmune Liver Diseases

Autoimmune liver disease has a spectrum of presentations, from the most common autoimmune hepatitis (AIH) to less common diseases among Saudi women such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) as well as rare forms of overlapping liver disease [6,78].

AIH

AIH is an immune-mediated liver disease that predominantly affects women [79,80]. The rate of disease progression in AIH is similar between men and women [80].

AIH is classified as either type I AIH, which is more common in adults, or type II AIH hepatitis, which is more common in children. AIH is diagnosed based on clinical, laboratory and histological features [80-82]. A diagnostic criteria for AIH was established and modified by the AIH group [83,84].

In Saudi Arabia, reports of AIH hepatitis show a similar female predominance of 65%-75.7%. All of the adult patients in the reported AIH data had type I AIH. More than 33% of the patients presented with advanced liver cirrhosis [6,78]. The association between AIH and other autoimmune diseases (mainly thyroid diseases and systemic lupus erythematosus) is common among Saudis [6,78]. The treatment response to steroids and immune suppression with azathioprine was favorable in Saudi women with AIH [6,78]. Liver cirrhosis secondary to AIH is a rare cause of HCC. In our report of HCC in Saudi Arabia, no cases of HCC were related to AIH [55,44]. AIH more commonly indicates liver transplantation in Saudi women than Saudi men 3 versus 13 out of 16 patients according to the report of Khalaf et al. [85].

PBC and PSC

PBC is a cholestatic liver disease that affects middle-age women 10 times more often than men. If left untreated, PBC causes

progressive hepatic damage and liver cirrhosis. Women are usually more symptomatic than men and complain of pruritus [86]. Despite the prevalence of PBC in women, HCC is more commonly reported in men with PBC than women [87], which further supports the protective effect of female sex hormones against HCC. However, the survival rate is similar between men and women [88]. Treatment with ursodeoxycholic acid effectively delays the progression of the disease and its hepatic complications [68,89]. Bone disease in the form of osteoporosis is another common feature of PBC, which causes symptoms and morbidity in affected patients [90]. Primary sclerosing cholangitis is a chronic cholestatic liver disease that causes progressive distraction and fibrosis of the intra- or extra-hepatic biliary system or both. It is more common in men and associated with inflammatory bowel disease, mainly ulcerative colitis. This disease responds poorly to therapy and ultimately progresses to decompensated cirrhosis and HCC [68,89].

Data on the other forms of autoimmune liver disease in Saudi Arabia are limited to sporadic case reports. These data do not suggest clear sex differences [90-92]. Extrapolated statistics on the PBC prevalence in Saudi Arabia was estimated to be 0.0034%. However, additional data are needed to confirm this statistics [93].

Metabolic Liver Disease

Hereditary hemochromatosis is a disease that is commonly reported among Caucasians. The hepatic manifestations of hereditary hemochromatosis result from an abnormal iron deposition in the liver [37]. Premenopausal women have lower blood ferritin levels than men. Ferritin levels in women peak after menopause [94]. Thus, women have a higher prevalence of anemia than men [95]. Male patients with hemochromatosis tend to have clinical manifestations earlier in life than women. This finding is attributed to blood loss in premenopausal women. Hepatic manifestations of hemochromatosis are more frequently reported in men [96]. Although Saudi Arabians are not Caucasian, a few sporadic cases of hemochromatosis have been reported in this population. A report of the prevalence of a hemochromatosis gene among a normal Saudi population from Jeddah found rates of 0.0% and 14% for C282Y and H63D, respectively [97].

Wilson's Disease

One report on Wilson's disease as an indication for liver transplantation revealed a male predominance of 7 of 16 compared with 9 of 16 females [98]. This finding is similar to data from Litwin et al., who showed a male predominance of Wilson's disease in Poland [99].

Vascular Liver Diseases

Budd Chiari syndrome

Budd Chiari syndrome is a disease of hepatic outflow at the level of the branches or major hepatic veins, inferior vena cava, or right atrium [100]. This syndrome can present in fulminant, acute or chronic forms [100]. In a report of Budd Chiari syndrome from King Feisal Hospital in Riyadh, Al Himali et al. showed that women represented only 33% of 43 patients with Budd Chiari syndrome over 10 years from 1990-2000 [101].

Alcoholic Liver Disease (ALD)

Excessive alcohol intake is a major cause of liver cirrhosis worldwide, and it affects men more commonly than women [37,68]. Evidence has shown that women are more prone to ALD at a lower

(but excessive) weekly alcohol intake of 336-492 g. The relative risk of developing cirrhosis was 7 in men and 17 in women [102]. Women with ALD also have a more rapid progression of fibrosis compared with men [103]. No substantial data on ALD have been reported in Saudi Arabia. In a report of liver disease among Saudis in 1966, Fashir et al. found that one patient out of 277 had ALD [104].

Liver Tumors

HCC

The male sex is an independent risk factor for the development of HCC in HBV-infected patients [105,106]. A male predominance in HCC has been shown worldwide [107]. A lower prevalence of HCC in women is likely partially because of the protective effect of estrogen against HCC [108]. Other possibilities for the male predominance were mentioned in the other sections of this report for liver disease, such as HBV and HCV infections and ALD, which are more common in men. On the other hand, most benign liver tumors are more common in women [68,109] including focal nodular hyperplasia and hepatic adenoma. Saudi reports on liver tumors have focused on HCC, which also shows a male predominance with figures of nearly 2/3 for male and 1/3 for female. An exception for that are patients with AIH. This finding is similar to data provided by Teufel et al. [30,55,110].

Liver Transplantation in Women

In general, advanced liver cirrhosis is more commonly diagnosed in men than women [4]. Women represent about 33% of liver transplantation recipients [111,112]. However, women show a better long-term post-transplantation survival rate [112]. Similarly, Saudi Arabian data show a general male predominance of 60%-80% for liver transplantation due to viral hepatitis or Wilson's disease [98,113-115]. However, AIH as an indication for liver transplantation was more frequent in women than men [85,116] Hepatocellular carcinoma as an indication for liver transplantation is more common in Saudi men than women (approximately 67% and 33% of all cases, respectively) [116]. On the other hand, women represent only 10% of all living liver donors [117].

The difference between males and females in the long term post liver transplant survival has not been addressed among Saudis.

Liver and Pregnancy

Apart from liver disease that can develop both in men and women with variable rates, certain liver diseases are unique to women. These diseases are reported during different stages of pregnancy to varying degrees. These include hyperemesis gravidarum during the first trimester, intrahepatic cholestasis of pregnancy during the late second and early third trimester, and preeclampsia, HELLP syndrome and acute fatty liver of pregnancy during the late third trimester [118]. The data on pregnancy-associated liver disorders in Saudi Arabia are limited, and they focus on the prevalence of viral hepatitis among pregnant women [73]. A previous study showed a prevalence of 1.6% for HBsAg [73]. Acute hepatitis was predominantly caused by Hepatitis E virus in approximately 50% of patients, followed by A-E acute hepatitis in approximately 31% [119]. This result differs from what other international reports of the predominance of acute HBV infection in pregnancy [120].

Shobaili showed that the incidence of intrahepatic cholestasis during pregnancy was 0.35% (76/21,960) in the Al Qassim region of Saudi Arabia [121].

Conclusions

The Saudi Arabian data show that the most common liver diseases among Saudis (chronic viral hepatitis B and C) affect men more often than women. On the other hand, AIH, which is frequently diagnosed in Saudis, is more common in women. NAFLD, which is increasingly recognized among Saudis because of the increased rates of diabetes mellitus and metabolic syndrome, showed a variable prevalence between men and women across different studies. Hepatocellular carcinoma is more often diagnosed in Saudi men than women.

Most Saudi liver disease reports are prevalence studies. More clinical outcome and prognosis data are needed to understand the in-depth differences among liver diseases between Saudi men and women.

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