

LIVER DISEASES: GLOBAL SCENARIO**Despair and Hope!**

Of late, liver diseases are being identified as leading causes of disability, disease and death globally. Liver deaths occur mainly because of 3 clinical situations namely i. liver cirrhosis presenting as end stage liver disease, ii. liver cancer or the Hepatocellular carcinoma, usually recognized late in the course or iii. acute liver failure also named as fulminant hepatic failure with high mortality and it would be prudent to breakdown global liver deaths under these 3 subheadings (Fig 1).

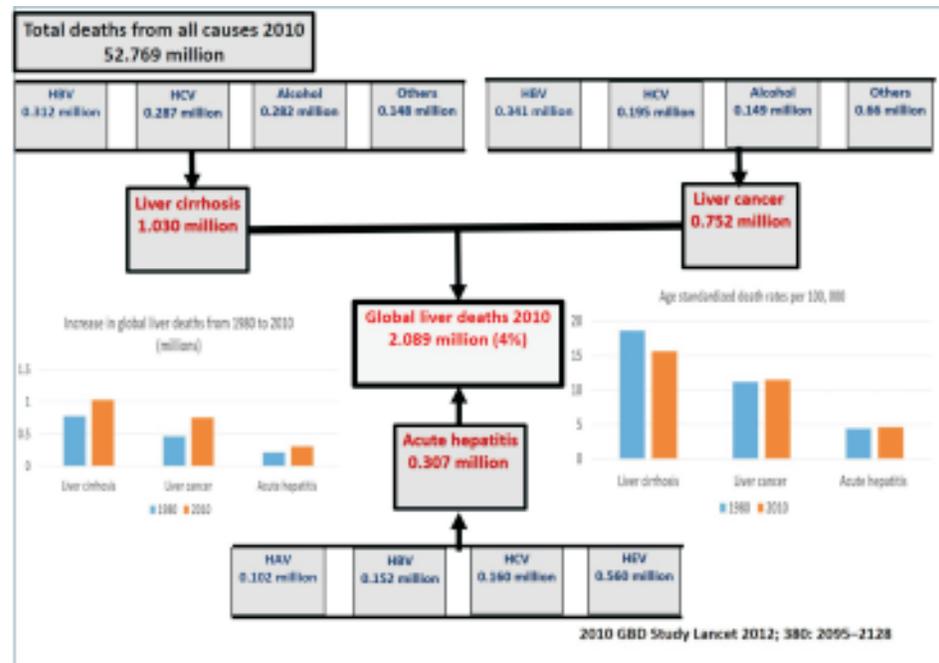


Fig 1. Global Deaths caused by Liver Diseases 2010.

Global liver disease data have been addressed in 2 landmark studies published recently. "Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (nicknamed as GBD 2010)" [Lancet 2012; 380: 2095-2128] estimated the annual global deaths between 1980 and 2010 for 235 disease states. In 2010, there were estimated 52.8 million deaths globally from all disease causes. Of course ischemic heart disease as expected ranked as number one cause of global deaths. Liver cirrhosis caused around one million (around 2%) of deaths in 2010 and ranked 17th in the causes of global deaths. Liver cancer and acute liver failure resulted in another one million deaths. If these estimated are to be believed, liver disease resulted in over 2 million deaths in 2010 which amounts to around 4% of global deaths. In another study, a systematic analysis of deaths from liver cirrhosis was estimated in 187 countries between 1980 and 2010 [BMC Medicine 2014, 12:145]. Again it was estimated that liver cirrhosis caused around one million deaths globally in 2010, confirming the data of GBD 2010 study. Disturbing is the data that unlike other major causes of mortality, liver disease deaths had increased over the years rather than declined. Liver diseases deaths had increased from 1.65 million in 1980 to over 2.0 million in 2010. In 1980, liver cirrhosis, liver cancer and liver failure

caused 0.77 million, 0.46 million and 0.21 million deaths globally which had increased to over one million, 0.75 million and 0.30 million respectively in 2010. Over the same period, the age-standardized cirrhosis mortality rate decreased by 22%. This was largely driven by decreasing cirrhosis mortality rates in China, the US and countries in Western Europe.

Liver diseases are a major cause of deaths in some countries. In 2010, Egypt, followed by Moldova, had the highest age-standardized cirrhosis mortality rates, 72.7 and 71.2 deaths per 100,000, respectively, while Iceland had the lowest. In Egypt, almost one-fifth (18.1%) of all deaths in males 45- to 54-years old were due to liver cirrhosis. Liver cirrhosis mortality in Mexico is the highest in Latin America. Mortality from liver cirrhosis was also comparatively high in Central Asia countries, particularly Mongolia, Uzbekistan and Kyrgyzstan, and in parts of sub-Saharan Africa, notably Gabon. In France and Italy, liver cirrhosis mortality fell by 50% to 60%; conversely, in the United Kingdom, mortality increased by about one-third. Liver disease is now established as the fifth most common cause of death after heart disease, stroke, chest infections and cancer.

What about our national scenario? According to the latest WHO data published in May 2014 Liver Disease Deaths in India reached 0.2 million or 2.44% of total deaths. The age adjusted death rate is 21.96 per 100,000 of population and ranks India 61 in the world among liver deaths. Many experts believe that liver disease is spreading like an epidemic in India with one in every five adults getting affected. In Mumbai alone, nearly 2000 patients die annually due to liver failure or liver cancer, while 300 patients are awaiting a liver transplant at any time.

In Kashmir, liver disease is taken its toll. There is an appreciable public concern about liver related deaths in our society. These deaths are mainly caused by increasing occurrence of liver cirrhosis and liver cancer. The story of epidemics of hepatitis E and resultant deaths in pregnant women has been focused by our group for last few decades and is a major healthcare problem in our community. Recently and shockingly, epidemics of hepatitis C is being seen in our community and our reports on this in few villages in South Kashmir are a glaring example. Hepatitis B and hepatitis C following transfusion of blood and blood products continues to be a problem in our community. This phenomenon is related to gross breakdown of primary to tertiary healthcare practices in our community.

What are the etiological causes of these 3 liver diseases leading to liver deaths? Major etiological players in this drama of disease and death were hepatitis viruses [hepatitis A to E] and chronic ethanol abuse.

HAV: Estimated 117 million people were infected with **31 million** symptomatic illnesses and **30,283** deaths (1990); Increase to 126 million with 35,245 deaths. Increase number in age groups 2-14 years and >30 years (2005)

HEV: Estimated 20 million hepatitis E infections, **3.4 million** symptomatic illnesses, **70,000** deaths and **3,000** stillbirths in 2005 [9 (71% world population) of the 21 GBD regions]

HBV: More than 2 billion people have been infected. Of these **240 million** are chronically infected and at risk of serious illness and death from cirrhosis and hepatocellular carcinoma. Between **500,000 and 700,000** people die annually as a result of HBV infection

HCV: Around **150 million** are chronically infected. More than **350,000** people are estimated to die from HCV-related liver diseases each year

HDV (..the vanishing disease..): Worldwide **15-20 million** people are infected with HDV wide varying prevalence depending on the region

Fig 2. Hepatitis Viruses: Disease and Deaths.

Today we have a large pool of chronic carriers of hepatitis viruses across the globe (Fig 2). Estimated numbers of Hepatitis B Virus (HBV) & Hepatitis C Virus (HCV) infected worldwide are staggering 350 million and 500 million respectively. Of the 40 million HIV carriers, 3 million are infected with HBV and 4.5 million with HCV. It is estimated that HBV results in one million deaths worldwide yearly and HCV causes whooping another million deaths. End Stage Liver Disease (ESLD) and liver cancer constitute major causes of deaths related to HBV & HCV infections. Fight against Hepatitis B and hepatitis C has shown 2 major breakthroughs. Firstly, there is a very effective vaccine against hepatitis B. Universal hepatitis B vaccination at birth in endemic areas has been shown to be highly effective in reducing carrier rates in children as well as the incidence of end stage liver disease and liver cancer. Today 182 countries have now included hepatitis B vaccination in national immunization program and we follow this in our EPI program aggressively to change the epidemiology of HBV in our country. Hepatitis C vaccine is a distant dream, however, there has been major breakthrough in the drug therapy of hepatitis C, making cure of this disease within armamentarium of a general practitioner. This game changer for hepatitis C would have a major impact on global burden of liver diseases caused by HCV in future.

Hepatitis E virus (HEV) has turned out to be the most enigmatic human agent since we discovered the agent in 1980. HEV causes large-scale waterborne epidemics in developing countries involving hundreds and thousands of adult populations. Around half to two-thirds of endemic hepatitis in such countries are caused by HEV. HEV has increased incidence and severity in pregnant women and is the commonest cause of acute liver failure in our society. In recent years, hepatitis E is recognized as a clinical problem in industrialized countries. HEV agent has entered in to food borne chain and is spread by consuming raw or undercooked pig livers available in super-markets in such countries. Recently we calculated HEV infections load globally. In 2005 an estimated 20 million incident HEV infections had occurred resulting in 3.3 million symptomatic cases, 70,000 deaths and 3000 stillbirths. In India alone, over 2.2 million cases of hepatitis E are thought to occur annually. Because of the impact of this infection globally it is imperative that measures be taken to control this python. Clean drinking water and safe sewage disposal are the corner stones of control, however, it may take years before we get to drink a glass of clean portable water in India. Two HEV candidate vaccines have successfully completed phase 3 trials and ready for the prime time. As of today, HEV vaccine 239 is available in China and is very effective in preventing hepatitis E virus infection and its long term effectiveness has been confirmed. (Fig. 3)

Agents HAV, HBV, HCV, HDV, HEV [unlikely to introduce another major alphabet]
Disease epidemiology: Well studied for all hepatitis viruses; identify evolving issues due changes in global scenarios [immigration]
Block modes of Transmission: Safe water/sewage disposal, safe syringe (IDU's/healthcare), safe mother/neonate, safe sex [major issues]
Primary protection: HBV vaccine, HAV vaccine, HEV vaccine (in the offering), HCV vaccine (Evasive)
Care of infection: Anti-viral agents (against HBV, HCV, HDV & HEV)-Cure of HCV has been a remarkable phenomenon
Care of ESLD/Liver cancer/Acute liver failure- extend care to primary care, liver units, transplant centers
Awareness of scope of problem: GBD study to assess disease load, Awareness programs, expanding the search, point-of-care testing
Funding for research/resources to low income countries: implement community program : Organizations, GAVI
<i>..a long way to go in care of viral hepatitis ..</i>

Fig. 3. Control of viral hepatitis: Now, then and in future.

Chronic alcohol abuse is an important player in the causation of chronic liver disease and liver related deaths. Globally, in 2010, alcohol-attributable liver cirrhosis was responsible for 0.5 million deaths and 14 million disability adjusted life years [DALYs], representing 0.9% of all global deaths and 0.6% of all global disabilities, and around half of all liver cirrhosis deaths and nearly half of all liver cirrhosis disabilities. Alcohol-attributable liver cancer was responsible for 80 thousand cases. These data stress the fact that burden of alcohol-attributable liver cirrhosis and liver cancer is high globally and entirely preventable. Interventions to reduce alcohol consumption are recommended as a population health priority and may range from taxation increases for alcoholic beverages to increases in screening and treatment rates for alcohol use disorders.

There has been a new kid on the block of whom we have to learn more about. Non-alcoholic fatty liver disease (NAFLD) has taken us by storm globally. The increasing incidence of NAFLD is tied to the obesity epidemic and the subsequent metabolic derangements brought along with it. In the United States, NAFLD is the most common cause of liver disease, representing over 75% of the chronic liver disease. It also is one of the most common indications for liver transplantation, contributing a major burden to both the morbidity and mortality of the nation. NAFLD is a disease of all ages, and the disease has been reported in children as young as 2 years of age. Results from prevalence studies done internationally have varied widely, with recent studies done in Japan and England indicating the prevalence of the disease has nearly doubled over the last twenty years. This increase was even more dramatic in adolescent populations, where the incidence increased 174%. Kashmir is in the middle of an epidemic of metabolic syndrome and NAFLD. NAFLD is a potentially progressive liver disease and shall pose serious health problem to our community in near future. What could be the possible reasons for introduction of metabolic syndrome and NAFLD in our community of late? For sure the focus has to be our changing sedentary life style and changing food habits. You might be shocked to know that a plate of wazwan shared by 4 persons served 40,000 kilocalories (Fig 4) and indulgence in this delicacy shall throw any body's metabolic system in to disarray and load liver with fat, similar to what binge drinking can do in the West. So if we need to fight this metabolic syndrome and liver disease caused by NAFLD, we need to be on roads and gyms rather than driving luxurious cars, go back to our delicious Haak (Cabbage) and rice rather than delicacy of Wazwan and maintain a body mass index at least under 25.

In view of the above there are many slogans in the air to address the increasing burden of liver disease globally, nationally and regionally in our society. First, awareness and early detection of disease and treatment in the primary care would help. This can be done by improved screening for hepatitis viruses in the community at various ages and at various levels. It includes screening school children, at entry to colleges, employment health checkup, high risk groups, pregnancy and through camps in the community. Expanding and targeting ultrasound detection of NAFLD in the community shall help to pick up this progressive disease early. Government health policies to reduce alcohol consumption, including a minimum unit price per unit of alcohol and health warnings on alcohol packaging, should be implemented. Deaddiction centers must be activated and work intensified and in Kashmir, work of such teams needed to be complimented. Total ban on Alcohol to as a tool to electoral catch and election slogan is welcome step. Bihar has taken lead and Tamil Naidu is threatening to implement it. Our civil society slogans are falling a deaf ear to our politicians in this Muslim majority state, where religious fervor could be added to delicate plate. Similarly, taxation on foods with high sugar content and the promotion of healthy lifestyles are recommended to reduce the number of patients with NAFLD. Wazwan in its original color and as a delicacy must continue in our society and serving 40,000 calories in one plate to cause binge eating to

the incumbents must stop. Civil society and administration have made inconclusive trials in the past and more people must enter this fray for a game change. Of course hepatitis B vaccination program and that of hepatitis A vaccination policy should be adhered to control these important pythons. There must be a dedicated attempt to introduce hepatitis E vaccine in our society and we must approach Chinese authorities to help us in this endeavor. Healthcare practices must improve to focus on hand washing, use of disposable syringes and use of safe blood and blood products.

Item	Description	Weight	Kcal	Fats	Proteins	Carbohydrates
Rice	raw item	1500 g	5000	7.5 g	100 g	990 g
Mutton	muscle	2750 g	4400	350 g	440 g	-
	visible fat	250 g	2250	250 g	-	-
Chicken	half	750 g	875	15 g	500 g	-
Cheese	One piece	60 g	200	15 g	10 g	4 g
Oils & oily substances	oils	250 g	2250	100 g	-	-
	ghee	750 g	6750	750 g	-	-
	animal fat	1500 g	13500	1500 g	-	-
Milk & milk products	milk	250 ml	167	5 g	8 g	11 g
	yoghurt	1000 g	600	40 g	31 g	30 g
Sweet dish	kheer	500 g	1640	23 g	46 g	223 g
Pullao	basmati rice cooked with dry fruits	300 g	1100	67 g	15 g	130 g
Cold drinks	Pepsi or coca cola	2000 ml	840	-	2 g	200 g
Grand total		11.8 kg	39572	3123 g	1152 g	1588 g
<p>The above figures were drawn from a random sample of 10 parties. The number of dishes served varied from 16 to 35 (median 23) and the mutton served per plate was from 2 to 5 kg (median 3 kg). The above data were calculated on mutton serving of 3 kg per plate.</p>						

Fig 4. Kashmiri Wazwan Plate with Dishes (items), their Description and Caloric Values, served for four persons

While all above practices are in the realm of society and healthcare and can be immediately put in to practice, the establishment of a specialized liver unit and liver transplantation has been haunting us in the State. Over the last several years we have been promised to start liver transplant in J&K and we have been looking forward to have our first patient with liver cirrhosis, liver cancer or acute liver failure to have label of "Liver transplanted at SKIMS". However, time has come to approach the politicians to support the establishment of an independent liver unit in the State, may be two to avoid controversies and start receiving, investigating and treating patients with liver diseases and transplanting those who reach the realm of end stage liver disease, liver cancer and acute liver failure.

Prof. Mohammad Sultan Khuroo, MD, DM, FRCP (Edin), FACP, Master American College of Physicians (MACP, Emeritus), Former Director, Professor and Head Gastroenterology Chairman Dept. Medicine, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, Kashmir, India; Former Consultant and Head Gastroenterology and Liver Transplantation, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; Director, Digestive Diseases Centre, Dr. Khuroo's Medical Clinic, Srinagar, Kashmir, India. E-mail: khuroo@yahoo.com; G-mail: mohammad.khuroo@gmail.com; Website: www.drkhuroo.com; Facebook: www.facebook.com/mohammad.khuroo; twitter: Mohammad Khuroo @mskhuroo

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