



CHRONIC KIDNEY DISEASE IN HEPATITIS B AND C PATIENTS: A SYSTEMATIC OVERVIEW

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Abstract— Developing countries like India face a unique challenge in managing disease like chronic kidney disease. Early detection and treatment is mandate to cope up with the renal failure and its comorbidities. In few of the cases development of hepatitis also occurs which further worsen the situation. Hepatitis being the blood borne virus affects the patient in most of the cases with renal failure. The advent of effective nucleotide analogs (NAs) has bid the chance to minimize the effects of hepatitis B virus (HBV) infection in HBV-positive patients with chronic kidney disease. Combination with immunosuppressive agents is most favorable in rapid renal function impairment. Other concern is the infection of hepatitis C virus (HCV). It represents a major medical and epidemiologic challenge in patients with renal replacement therapy with dialysis or transplantation. In this scenario the presence of HCV correlates with higher rates of mortality than in HCV-negative subjects on dialysis or undergoing kidney transplant poses a major concern. Thus, the present review deals with the basics of CKD and its correlate with the hepatitis. Further we will also look into the effect of hemodialysis on hepatitis patients and their major concerns.

Keywords— Renal disease, Chronic Kidney Disease (CKD), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Hemodialysis

I. INTRODUCTION

The renal failure with its high prevalence, morbidity and mortality, is an important public health issue to deal with. In most of the developing countries like India, there are large numbers of patients below the poverty line who suffer with the low monetary allocations for health care and thus, it adds to the health problem along with the metabolic alterations.

Diseases like renal and hepatic diseases are also ignored in front of communicable infections as they may cause epidemic conditions in the society [Appel et al. (2005)]. Kidney failure is also known as an end-stage renal disease (ESRD) which is the, last stage of chronic kidney disease. The

condition notifies when the kidney have stopped working well enough for patient to survive without dialysis or a kidney transplant. The damage is not a one-day process, it occurs over a long period of time. In earlier days it remain asymptomatic but in later stages the condition may get worsen and kidneys are less able to do the job and this is clinically defined as chronic kidney disease (CKD).

To cope up with renal complications hemodialysis is a frequently used measure. The patients undergoing hemodialysis are at much higher risk of developing blood borne infections such as HBV and HCV due to prolonged vascular access and a longer period of exposure to contaminated equipment. The symptoms of hepatitis are more common in dialysis patients as compared to non-dialysis patients [Tang et al. (2005), Furusyo et al. (2000), Fabrizi et al. (2010)]. Symptoms were found to be more constant with the age and number of transfusion products [Furusyo et al. (2000)]. Similar to HCV, it was studied for hepatitis B virus (HBV) which also has a complex relationship to kidney diseases. It was studied with chronic HBV infection that it plays an etiologic factor in secondary glomerular diseases. The HBV patients pose a critical impact on the clinical management of kidney transplant recipients and patients with renal diseases who are treated with immunosuppressive drugs. In this review chronic kidney disease is discussed followed by hepatitis and its effect on hemodialysis patients.

II. CHRONIC KIDNEY DISEASE (CKD)

Chronic kidney disease refers to a state where the kidneys are damaged and have lost their potential of filtration, thus unable to filter the blood in appropriate manner. The chief risk factors for developing kidney disease include diabetes, high blood pressure, heart disease, and a family history of renal failure [Rajapurkar et al. (2012)]. Demographic data presented by United Nations Children's Emergency Fund show that amongst total population 28% of children are 2.5 kg at birth leading to hypovitaminosis A and other nutritional issues causing reduction in kidney volume at birth and a lower eGFR [Varughese et al. (2007)]. Issues like poverty, poor sanitation, pollutants, water contamination, overcrowding, and nephrotoxins may lead to glomerular and interstitial kidney diseases. Apart from these genetic conditions like

hypertension and diabetes mellitus further worsen the condition. Due to poor availability of diagnostic tools and challenges in access to care almost 50% of patients with advanced CKD are reported when the eGFR is, 15 ml/min per 1.73 m². This high percentage for grounds the need for full-bodied screening programs for those at risk for CKD. The reported prevalence of CKD in different regions ranges from, 1% to 13%, and recently, data from the International Society of Nephrology's Kidney Disease Data Center Study reported a prevalence of 17% [Ene-Iordache et al. (2012)].

III. STAGES OF CKD AND GFR RANGE

Glomerular filtration rate (GFR) is the most accurate assess of kidney function. It is calculated by using the person's age and their serum creatinine level. Creatinine is obtained from blood report as it is a waste product that comes from muscle activity.

According to the GFR rate the practitioners divide CKD in five stages. The stages and their calculation are summarized in the table:

Table 1: Stages of Chronic Kidney Disease and their Glomerular Filtration Rate (<https://www.disabled-world.com/health/cancer/kidney/gfr-ckd.php>).

Stage 1	Normal or high	GFR > 90 mL/min
Stage 2	Mild CKD	GFR = 60-89 mL/min
Stage 3A	Moderate CKD	GFR = 45-59 mL/min
Stage 3B	Moderate CKD	GFR = 30-44 mL/min
Stage 4	Severe CKD	GFR = 15-29 mL/min
Stage 5	End Stage CKD	GFR <15 mL/min

When kidneys are working well, they remove creatinine from the blood. As kidney function slows, blood levels of creatinine rise. The disease usually get worse slowly, and the patient is asymptomatic until kidneys are badly damaged. In the subsequent stages of CKD the patient also may notice symptoms that are caused by waste and extra fluid building up in the body. The usual symptoms developed may be depicted as follows:

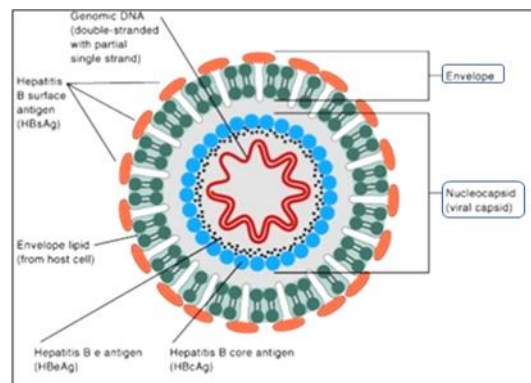
Figure 1: Symptoms of Chronic Kidney Disease



IV. HEPATITIS B VIRUS (HBV)

The structure of hepatitis virus consists of nucleocapsid involved in packaging of viral genome which is approximately 28 nm in size and comprises core antigen. The membrane encapsulating the Dane particle is derived from secretory pathway via Golgi apparatus and endoplasmic reticulum. Outer membrane envelope forms HBsAg which poses the antigenic property by forming complex antigenic determinant. It contains three viral surface proteins named according to their size of small, middle and large as HBsAg, HBmAg and HBiAg respectively. While studying the molecular basis of its structure it was found that they are coded by the same ORFs as of start codon and get overlaps with polymerase ORF [Seeger et al. (2000)]. Template for replication is served by the pregenomic RNA. Viral polymerase is the only enzyme encoded and is also located in the nucleocapsid [Summers et al. (1982)]. The structure of hepatitis virus is depicted in the figure underneath: (Sherris Medical Microbiology, 7eChapter 13: Hepatitis Viruses).

Figure 2: Structure of Hepatitis B Virus



Another translation product of core gene include hepatitis B envelope antigen (HBeAg). For the translation of HBeAg, an upstream pre-core region with ATG codon is required [Tong et al. (2012)]. The HBeAg is an important component in the diagnosis of HBV infection which acts as an active marker for viral replication [Chen et al. (2004)]. As visualized in the image virus contains two DNA strands:

- long [L (negative) strand] fixed length of 3.2 Kb
- short [S (positive) strand] the length is variable at its 3' end. The S strand usually spans 50% to 100% of the length of the L strand.

➤ Epidemiology of HBV

Hepatitis B as is previously discussed a blood-borne virus spread through percutaneous or mucosal exposure to infected blood or body fluids [Baijal et al. (2014)]. According to recent studies there are more than 350 million people worldwide with chronic hepatitis B (CHB) infection [Saravanan et al. (2008)]. India lies in the intermediate endemicity zone with the



prevalence of 2–7%, with an average of 4% and a disease burden of about 50 million. Most vulnerable population is found in the tribal areas where due to low awareness rate the high burden is maintained through intercaste marriages, customs, illiteracy and miserable health care resources. The mode of transmission of chronic hepatitis B (CHB) in India is horizontal transmission in early childhood (mostly from family contacts) and to lesser extent by perinatal transmission. The risk factors may include contact of cut skin or mucous membranes with tears, saliva or blood containing HBV-infected secretions. The age of acquisition of HBV is an important determinant of outcome; the earlier the age, the higher the risk of chronicity.

The disease is known to occur in three stages during its natural history –

- (a) Immunotolerant phase: in this the HBe is +ve and high DNA load with normal enzymes
- (b) Immune active phase: with heave in enzymes, hepatitis B e antigen (HBeAg) negativity and clearance of DNA, and
- (c) Inactive carrier phase with development of HBe antibody (antiHBe), normal enzyme levels and negativity for HBV DNA.

The possible causes of lasting viral infection are due to high viral load, rapid replication, viral inhibition of antigen presentation, viral mutations that antagonize antigen recognition, immunosuppressive effects of virus etc. [Sprengers et al. (2005)].

➤ **HBV in renal disease**

During the study of renal failure it was sometimes visualized the case of chronic HBV infection. Manifestation of the disease is by immunity mediated glomerulopathy in which the virus particles are identified in different areas of glomeruli. For treatment of HBV-associated renal disease KDIGO (Kidney Disease: Improving Global Outcomes) indicated that patients should be treated according to standard clinical practice guidelines for HBV infection. The latest meta-analysis [Pipili et al. (2013)] on handling of HBV-associated glomerulonephritis reasoned that the combined therapy of antiviral and immunosuppressant is an effective regimen without hindering the HBV replication or damaging liver and renal function [Srivastava et al. (2013)]. Next step is to determine the therapy which should always be made on an individual basis via a multidisciplinary approach decided by the patient’s age, baseline viral levels, type of renal disease, risk of resistance, and drug renal protective profile. For all the patients with chronic HBV infection long-term NA therapy is generally recommended irrespective of the presence of renal disease. In some of the cases NA therapy may be discontinued like:

- patients with HBeAg positive chronic HBV infection who achieve stable HBeAg seroconversion and HBV DNA undetectability for at least 12 months

- In patients with HBeAg-negative chronic HBV infection who achieve HBsAg loss.
- The maximal tenure of antiviral therapy for HBV-associated nephropathy is not specific it varies person to person and in most of the cases long-term antiviral treatment is recommended. Some of the commonly used drugs are tabulated as under: [Zheng et al. (2012)].

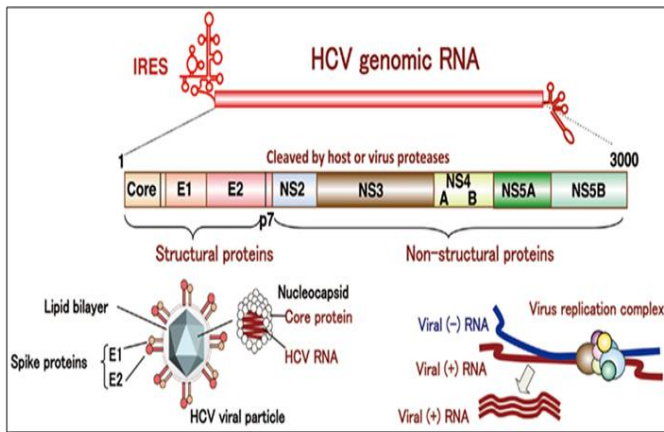
Table 2: Drugs for HBV Treatment

Drugs	Effect
Telbivudine	favorable effect on renal function [Gane et al. (2014)]
Entecavir	resistance profile in NA-naive patients and has been reported to be safe and effective in a few patients with HBV-related glomerular disease [Numata et al. (2011)]
Tenofovir and Emtricitabine	HIV–HBV coinfectd patient with membranous nephropathy [Guillevin et al. (2005)]
Rituximab	for suppression of vasculitis—and plasma exchange (European Association For The Study Of The Liver)—for removal of circulating immune complexes— may be gainful for ameliorating kidney function and disease manifestations

V. HEPATITIS C VIRUS (HCV)

Genome size of HCV is 9.5 Kb with conserved untranslated regions on both 5’ and 3’ termini of the genome. The UTRs are further flanked by a large translational ORF which encodes polyprotein of 3000 amino acids. Its structure contains an uncapped 5’ noncoding region, of approximately 340 nucleotides, comprises of internal ribosomal entry site (IRES) which is essential for cap independent translation of viral RNA. The 3’ region of the genome contains noncoding regions. The polyprotein encoded by the genome is later co and post transcriptionally processed by various cellular and viral enzymes [Moradpour et al., Dalekos et al. (1998)] The detailed molecular structure is depicted in the following figure: [Kohji et al. (2012)].

Figure 3: Molecular structure of Hepatitis C Virus



➤ Epidemiology of HCV

Though the variations are found in studies across the geographical regions, the prevalence of HCV infection in India is about 1–1.9% [Sievert et al. (2011)]. In a population-based study performed by Chowdhury et al. from West Bengal, 3579 individuals were preselected and the seroprevalence of HCV antibody positivity was noted in 0.87%. The prevalence showed an enhancing drift from 0.31% in children aged below 10 years to 1.85% in adults aged 60 years or more [Chowdhury et al. (2003)]. Similar study conducted in New Delhi, 28,956 healthy blood donors were tested and the prevalence of anti-HCV was noted in 0.66% [Pahuja et al. (2007)]. The prevalence is more in HCV infection in high-risk group of patients like those receiving blood transfusions (patients with thalassemia major), subjects with IVDU, HCWs, subjects on hemodialysis (HD) is expected to be higher than in general population. In a study by Chakravarti et al. (2013) from New Delhi, 51 patients with anti-HCV positivity were enrolled and iatrogenic procedures were found to be responsible for transmission of HCV in 83.3% of patients with blood transfusion alone responsible in 67%. Jasuja et al. (2009) in their study on 119 patients receiving HD noted HCV infection in 27.7%. Longer duration of HD and getting HD at more than one centre are deemed important in acquiring HCV infection.

Genotype 3 is among the most frequent genotype reported in India accounts for 54–80% of cases. [Verma et al. (2008)] Studies from northern, western and eastern parts of the country have uniformly shown predominance of genotype 3; however, in southern India, both genotypes 1 and 3 HCV are found to be prevalent. [Narahari et al. (2009), Chandra et al. (2007)].

➤ HCV in renal disease

It was found through biochemical evaluation that the level of ALT (alanine aminotransferase) in HCV infection considerably increases in serum, thus it is considered a nonspecific marker of liver damage. Although ALT concentration is a molecular marker for hepatitis it is rather

weak for patients with renal failure due to vitamin B6 deficiency, presence of uremic toxins, or UV-absorbing components in the blood that could interpolate the transaminase sensing [Schneeberger et al. (1998)]. The presence of anti HCV antibodies by ELISA allows rare false-negative results in dialysis patients [Poynard et al. (2003), Pawa et al. (2007)] but is not efficient in characterizing acute and chronic infection. Quantitative determination of viral load is also an effective prognostic tool for the infection because patients with high initial HCV RNA levels benefit more from 48-wk treatment [Özgiir et al. (1996)]. For diagnosis and treatment of the infection following options are being looked upon:

- IFN treatment [McHutchison et al. (1998)]
- Liver biopsy provides key information on the extent of HCV associated hepatic disease, but requires caution in CKD because of the potential low risk of bleeding complications, especially in patients with chronic kidney diseases [Pawa et al. (2007)]
- Transjugular biopsy
- Noninvasive method like fibroscan showed a better diagnostic performance in hemodialysis and renal transplant patients with HCV infection [Varaut et al. (2005)].

VI. HEMODIALYSIS AND VIRAL HEPATITIS

The patients with higher levels of creatinine are directed for hemodialysis. Due to blood borne viral particles of HBV the prevention is necessary. The instauration of HBV & HCV immunization has importantly depressed the incidence in several indigenous regions [Fabrizi et al. (2015)]. Although immunized some of the patients show the presence of virus. For management of these patients undergoing hemodialysis, physicians keep continual checkup of blood and viral markers. Moderate or no elevations of serum aminotransferases are due to altered inflammatory response, and hence the lower serum HBV-DNA and HCV-RNA levels are the removal of blood by hemodialysis [Tseng et al. (2008)]. All these parameters may affect the clinical and laboratory presentation and course of chronic viral infection and the patient's response to antiviral therapy. The optimal therapy for chronic HBV infection on hemodialysis may involve observation, IFN-a, or NAs.

The eradication rate of HCV infection by antiviral therapy is high in hemodialysis patients rather than in those with normal renal function [Meyers et al. (2003), Zeuzem et al. (2000)]. The reason behind it is possibly the high antiviral drug plasma levels developed due to decreased renal clearance. It is noticed in the patients that the penetration of PEG-IFN is reduced by 45% in patients with ESRD [Thévenot et al. (2004)], due to the permeability and pore size of dialyzers. This may further lead to co-morbidities in dialysis patients [Barril et al. (2004)]. It was analyzed that if initially the viral load is low then the therapy of SVR works in a much better way. Combination of ribavirin with PEG-IFN is believed to be the best criterion of therapy in HCV-positive patients with normal renal function



up to 50 to 60% [Kes et al. (2007)]. Although the physicians hesitate to use the combination in person with dialysis for the adverse effects of the drugs like hemolytic anemia, that can be exacerbated in the presence of ESRD [Fehr et al. (2004)].

Apart from all the therapies and drugs studied for the treatment, role of diet is also found to be very necessary. In one of the study performed by Amardeep et al., it is found that malnutrition is a frequent and integral component of acute as well as some of the chronic diseases including hepatitis and CKD. Therefore, every patient should have an assessment of their nutritional status. Patient with advanced liver or kidney infection commonly have malnutrition but its assessment is confounded by many of the usual indicators of nutritional status. Thus, we may see that the patients undergoing dialysis are more susceptible to the infection somewhere due to comorbidities the adverse effects of drugs well as lower nutritional status and lack of awareness of the subject.

VII. CONCLUSION

Kidney and liver play an essential role in maintaining the metabolic functions in body. The kidney being important for ultrafiltration if is chronically damaged may also inhibit the function of liver in some or the other way. The CKD patients possessing higher value of creatinine underwent dialysis. These patients further due to blood borne infection carry higher chances of hepatitis infection. Thus the combinatorial drugs, healthy lifestyle and restricted diet are essential to make their life easier.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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