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RISK FACTORS INVOLVED IN HEPATITIS D INFECTION AND ITS MANAGEMENT: A REVIEW

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Abstract

Hepatitis D is a wide spread viral infection caused by HDV (Hepatitis D virus) and considerable community health concern in endemic area worldwide. Hepatitis D infection can be acute and chronic and it rapidly develops to chronic illness including fibrosis, cirrhosis, hepatic malignancy and hepatic failure. The spread of HDV-infection worldwide, in the regions are, including South America, Asia, Eastern Europe and Middle East. Countries such as Pakistan, Afghanistan, Turkey, India and Mongolia. Various risk factors lead to its spread such as chronic Hepatitis B, lacking HBV vaccination, occupational needle pricks, ongoing hemodialysis therapy, unsterilized dental interventions, use of intravenous drug, human migration, low socioeconomic and demographic factors, lack of routine screening further increase infection susceptibility. Successful management of Hepatitis D infection requires precise diagnosis, immediate medical care and suitable preventive measures. Diagnosis of HDV occurs through chemiluminescence immunoassay and real time polymerase chain reaction. Therapeutic option includes use of antiviral, (Pegylated interferon alfa, nucleos(t)ide and Bulevirtide). It can be preventing by following effective infection control procedure, using sterile medical instrument, safe injection practice and good laboratory practices.

Keywords: *Diagnosis, Hepatitis, Management, Prevention, Risk Factors, Treatment*

INTRODUCTION

Hepatitis D infection is a severe liver inflammation caused by Hepatitis D virus also known as delta virus. The Hepatitis D virus (HDV) is a satellite virus which requires Hepatitis B virus (HBV) for producing it envelop from hepatitis B surface antigen (HBsAg), helps its entry into hepatocytes (1).

Hepatitis D virus (HDV) can cause short term, as well as long term illness. If the infected individual cannot clear the infection, then it rapidly progresses to long term liver complication such as liver fibrosis, liver cirrhosis, (HCC) hepatocellular carcinoma and liver failure (2).

Generally, the Hepatitis D virus (HDV) is a blood borne virus; Its transmission occurs through contact with contaminated blood and blood products. The other routes of infection are including re- using of infected syringes/needle, accidental pricks with contaminated needles and use of unsterilized medical and surgical instruments. (3).

Hepatitis D infection is widespread worldwide and remains a significant public health challenge globally. The HDV is affecting millions of people and causes number of deaths. It is estimated that 12 to 72 million people are affected from Hepatitis D virus (HDV) worldwide (2). However, it is noted approximately 5% of chronic HBV carrier are affected with Hepatitis D virus (HDV), it indicates millions of individuals are at risk globally (4). Since HDV is recognized one of the worst forms of viral liver disease which rapidly progress liver complication such as cirrhosis, liver carcinoma and liver failure. It is observed around 80% of infected patients with Hepatitis D develop chronic hepatitis and progress to liver cirrhosis

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within 5 to 10 years (5). The Hepatitis D virus (HDV) is responsible for 18% of cirrhosis and 20% of HCC (Hepatocellular Carcinoma) (6).

Hepatitis D infection shows wide geographical variation and is endemic in several regions, such as parts of Middle East, Asia, South America and Eastern Europe. Countries including Pakistan, Iran, Afghanistan, India, Turkey and Mongolia due to high prevalence of Hepatitis B infection and reduced protective healthcare procedures (7**).**

PREVALENCE OF HEPATITIS D INFECTION IN PAKISTAN

Pakistan account for high burden of Hepatitis D infection across the world. Based on earlier epidemiological studies (1994-2001), the national anti-HDV prevalence was observed 16.6% among HBV infected individuals, the sample size was 1444 and 8721 were reactive (10). A study carried out in 2007 to 2008, identified the prevalence of anti-HDV 58.66%, (n=212/362) among HBsAg -positive individuals, who were attended liver clinics in Jacobabad and Karachi (8).

PREVALENCE OF HEPATITIS D INFECTION IN BALOCHISTAN

Balochistan is historically has been consider as a province with high burden of HDV infection among Hepatitis B-infected individuals. However, the data fluctuates markedly based on the geographical location (9). According to a study of 2007-2008, within HBsAg-positive patients in liver clinics of Jacobabad and Karachi, observed anti-HDV prevalence in Quetta 65.21% (n=15/23) and Naseerabad 60.0% (n=21/35). The most troubling finding comes from the eastern agriculture corridors and rural belt of the Balochistan, specifically in Jaffarabad where, the prevalence rate of anti-HDV was observed 65.4%, sample size was 55 and out of which 36 were positive (8). Furthermore, community based molecular study conducted in the Dera Allah Yar and Usta Muhammad towns during November-December 2021, (prevalence of active Hepatitis D) was observed 58.1% (n=108/186) and 67.1% (n=186/277) antibodies within Hepatitis B carriers. (9).

PREVALENCE OF HEPATITIS D INFECTION IN TURBAT

Turbat is located in Balochistan which is a well-known region for viral Hepatitis. However, where Hepatitis B is common and also cases have been reported for Hepatitis D infection but the real burden and actual prevalence is still unknown due to limited studies (10).

Despite global action to control Hepatic viral infection, Hepatitis D remains a neglected viral infection in several countries. Weak screening programs, low vaccination of Hepatitis B and lack of awareness lead the continued infection. Therefore, Hepatitis D infection remains a major public health problem, which requires early diagnosis, strengthened surveillance and preventive strategies globally (11).

RISK FACTORS INVOLVED IN HEPATITIS D INFECTION

Hepatitis D infection remains a critical public health problem, especially in areas where Hepatitis B infection is endemic. As Hepatitis D virus (HDV) is basically depends to HBV surface antigen for completing its life cycle and transmission (12**)**. It is observed the patients with chronic Hepatitis B infection are at high risk for Hepatitis Infection (13). Several socioeconomic factors (poor housing, low income, low education), demographic factors (gender, age, marital status), health-care related and behavioral factors are linked as well as increase the chance of Hepatitis D (14-17).

ROLE OF ACTIVE CHRONIC HBV CARRIER STATUS & HBV SUPPRESSION WITH ELEAVATED IN HEPATITIS D INFECTION

It is the absolute primary prerequisite, patients with chronic Hepatitis B virus (HBV) are strongly susceptible to a Hepatitis D Virus (HDV) co-infection (acquiring HBV and HDV from once exposure), by providing HBsAg for entry to hepatocytes (18, 19)**.** Once HDV enters a liver cell then it rapidly replicates and progress to chronic phase in 80% of cases (13).

Suppression of Hepatitis B replicates by the elevation of ALT enzyme with uniformity of microbiological penetration with the liver cell through infected HBV which can stimulate the HDV infection

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(19-21). However, in the case of chronic HBV suppress the level of DNA by elevated ALT spikes penetration in the liver cell, so the HBV goes in silent (dormant phase which is called window period) and the acute Hepatitis D inflammation starts (22).

ROLE OF ABSOLUTE (HBV) NON-IMMUNITY & UNVACCINATED PROFILE EFFECT IN HEPATITIS D INFECTION

Persons who are not immunized against HBV due to previous exposure or unvaccinated status are at high risk for prompt superinfection (occurs when an individual has chronic Hepatitis B), so the exposed liver cell are totally vulnerable to Hepatitis B entry, to Hepatitis D (18, 23). However, the body often triggers an enhanced immune response successfully clears both in 95% of adult person but the active phase may be most severe due to simultaneous hepatocyte destruction (2).

Unvaccinated status is a critical and most important indirect source for the spread of Hepatitis D infection. As Hepatitis D virus (HDV) is associated with HBV, if the individuals who are not immunized against Hepatitis B, remain susceptible to Hepatitis D. The inadequate immunization programs and missed birth vaccination increase the risk of Hepatitis B presence in the general population, thus contributing to Hepatitis D transmission (HDV) transmission (19, 20).

ROLE OF PWID & DRUG PARAPHERNALIA IN HEPATITIS D INFECTION

Reusing syringes or needles is traditionally one of the important routes of transmission of Hepatitis D virus (HDV) and has contributed to global highest rate of Hepatitis D. The remaining microscopic blood drops in needles, syringes can contain millions of viruses, re-using equipment contributes directly to the introduction of virus through intravascular system (24). Beyond direct needle-sharing exposure, the repeated use of non-needle drug-preparation equipment (paraphernalia) demonstrates a primary parenteral route for acquisition of Hepatitis D virus (HDV). It can place chronically HBV-infected patients at higher risk for superinfection (25).

ROLE OF ACCIDENTAL, OCCUPATIONAL NEEDLE STICKS & LABORATORY/HEALTHCARE WASTE MANAGEMENT IN HEPATITIS D INFECTION

Laboratory personnel and healthcare professionals may experience work-related exposure to blood-transmitted pathogens through accidental contact with infected blood, particularly following percutaneous and needlestick injuries. However, such occupational exposure can contribute to a potential route of transmission of Hepatitis D virus (HDV) (26).

Improper waste management of healthcare settings and laboratories can increase the risk of blood-borne transmission of pathogens such as Hepatitis B along with Hepatitis D. improper handling segregation, transportation and disposal of infected blood samples, sharps and laboratory waste raise the risk of sharps injuries, which promote the transmission of HBV beside Hepatitis D among waste handlers, healthcare workers and nearby communities (27, 28).

ROLE OF HEMODIALYSIS THERAPY & NON-STERILE DENTAL INTERVENTION IN HEPATITIS D INFECTION

Individuals are receiving regular dialysis are at higher risk of Hepatitis D infection because of repeated vascular punctures and possible exposure occur due to clinical settings. However, cross-contamination may occur if aseptic procedures are compromised or hemodialysis instruments are improperly disinfected, facilitate HDV transmission (29, 30).

Inappropriately sterilized dental procedures such as root canals or dental surgery, may act as a potential source of HDV transmission. Being a blood-borne virus HDV easily transmit via blood-to-blood contact through infected dental instruments which are used without standardized sterilization between patients (31, 32).

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ROLE OF DEMOGRAPHIC AND SOCIECONOMIC FACTORS IN HEPATITIS D

Demographic factors such as sex, age and geographic origin affect the distribution and epidemiology of HDV infection (33). According to many studies, Hepatitis D is more common in men as compared to female, which may be the result of work-related exposure, medical care-seeking behavior and through alcohol consumption or intravenous drug users (34). Furthermore, Hepatitis D is observed in every age group but most affected age group in between 20 to 50. Primarily this can be due to life time accumulated exposure of Hepatitis B infection and Hepatitis D infection risk factors, occupational exposure, other social activities and traveling or migrating for job purpose and where HBV is more prevalent (35,36). However geographical areas are also important characteristic (35). Since Hepatitis D virus (HDV) prevalence vary from region to region, traveling toward high endemic region such as Middle East, Central Asia, Amazon and Eastern Europe have a greater chance of Hepatitis D exposure. Thus, demographic factors play a great role for the distribution and high burden of Hepatitis D infection worldwide (4).

The low socioeconomic determinant is also indirectly linked with HDV infection which increases the chances for acquiring Hepatitis D by raising HBV exposure, limiting access to HBV vaccination, limiting screening, delaying diagnosis and limiting treatment. The factors include poverty, low education level and poor general health and malnutrition. Thus, socioeconomic conditions play great role for the distribution of Hepatitis D (15). Poverty is a key low socioeconomic factor which is linked with Hepatitis D infection. However, the people living under limited financial resources often have poor access to health, Hepatitis B vaccination, diagnostic services and safe medical procedure. Furthermore, in high prevalent areas poverty leads to the persistent circulation of Hepatitis B and resulting Hepatitis D (37). Inadequate education is also one of the vital socioeconomic determinants that indirectly increase the possibility of HDV infection (36). People with low education levels usually have lower health education and may not be aware about the Hepatitis D virus (HDV) and its transmission and prevention. Thus, poor health education contributes the reduced screening for HBV, late diagnosis which progress the infection to much complications and increase the risk of HDV (38). The Malnutrition also has indirect role for Hepatitis D infection due to weak immune system which make person higher vulnerable to infections (15).

ROLE OF DIRECT DOMESTIC HOUSEHOLD CO-HABITATION & PRISON/CLOSED SETTING POPULATION IN HEPATITIS D INFECTION

Living in prolonged and closed contact a with Hepatitis D carrier in the same household may raise the risk of Hepatitis D transmission, especially in regions where Hepatitis D infection is endemic and sanitation practices are insufficient (39). Although Hepatitis D virus (HDV) is not transmitted through casual contact but prolonged household contact can contribute to exposure to contaminated body fluids or blood through sharing personal items including nail clippers and razors. Since Hepatitis D virus (HDV) is depending to Hepatitis B virus for infection, family members who are infected with HBV are especially susceptible to acquiring Hepatitis D infection (40).

Prisons and other closed setting populations such as Drug rehabilitation facilities and jails, present an opportunity for the transmission of blood borne viruses (BBVs) such as HIV, HCV, and HBV which HDV is co-infection of HBV (41). According to many studies people in prisons have high prevalence with BBVs because of high-risk practice such as sharing of sharp objects, unsterile tattooing, intravenous drug use and inadequate access to healthcare facilities which increase the chance of transmission of infection. Additionally, lack of screening and weak infection-control procedures in prisons and jails facilities the spread of Hepatitis B as well as Hepatitis D within inmates (42).

ROLE OF HUMAN MIGRATION IN HEPATITIS D INFECTION

The increase in HDV infection is also linked with migration, particularly among people traveling to regions where HBV is endemic. Refugees, migrants or displaced populations are at high risk because of limited availability of healthcare services and inadequate screening facilities. However, the mobility of infected persons from high to low prevalence regions facilitates the spread and introduction of Hepatitis D

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in new demographic group. Furthermore, in several developing geographic areas, like Middle East and some region of South Asia, where migrated people are linked with increased HBV/HDV transmission, particularly in congested housing condition such as temporary settlements and refugee camps (43).

ROLE OF HOST-RELATED FACTORS, CHRONIC ALCOHOL ABUSE & CONCURRENT HIV CO-INFECTION IN HEPATITIS D INFECTION

It plays major role in the advancement and extent of Hepatitis D. As Hepatitis D virus (HDV) requires helper (HBV) to concluding its life cycle, the health consequences depended viral characteristics as well as other host- factor such as sex, age, genetic susceptibility, immune status and metabolic conditions. The patient with older age, impaired immunity or other chronic diseases including obesity, diabetes which are more probable to develop severe liver complications such as cirrhosis and hepatocellular carcinoma. In addition, host genetic diversity that controls the immune responses may affect susceptibility to chronic Hepatitis D infection and disease development. Thus host-associated factors are the major determinants of disease severity, persistence and clinical outcomes in Hepatitis D infection (44, 45).

Long- time alcohol consumption is also risking factor that cause severe liver damage in Hepatitis D infected individuals. However, alcohol consumption itself cannot transmit Hepatitis D virus (HDV) but markedly enhance liver injury, liver inflammation and liver fibrosis in infected person. The synergistic effect of viral infection and alcohol- induced hepatic toxicity raises the risk of rapid development to cirrhosis, liver deterioration and Hepatocellular carcinoma and even death if left untreated (2).

Human immunodeficiency virus (HIV) causes a decrease in the T lymphocytes +CD4 which impairs cellular immunity. This reduced immune response makes highly incapable body to control the Hepatitis D infection, thereby lead to more liver complication (46).

ROLE OF INADEQUATE PUBLIC HEALTH SURVEILLANCE SYSTEM & LACK OF ROUTINE SCREENING IN HEPATITIS D INFECTION

Grossly the spread of HDV infection, due to the limited surveillance result un-diagnoses/ incomplete reporting of HDV infection occur. In this way large number of HBsAg-positive patient remain unscreened for Hepatitis D as a result missed cases occur and the untimely detection of infected patient contribute continuous transmission among the community (4). On the other hand, the inadequate surveillance systems may understate the exact burden and prevalence of Hepatitis D infection and limit the recognition of high-risk populations and monitoring of outbreaks. Furthermore, the inadequate laboratory capacity and absence of reporting hinder early public health measures and it play an important role in the continuation and spread of HDV infection. Therefore, strengthening surveillance through regular Hepatitis D testing better reporting systems and implementation within national hepatitis program is crucial for preventing and controlling HDV (47).

Lack of routine screening is a well-known contributor to the persistent transmission, late diagnosis and under-assessment of the real burden of HDV infection. Since Hepatitis D infection occurs in chronic HBV carrier, failure to regularly screen Hepatitis B surface antigen positive patients and other high-risk populations including movement from endemic areas, intravenous drug users and individual with HIV. As a result, infection remains unrecognized and progress to liver complications (48) According to a study which was conducted during 2016- 2021, the chronic Hepatitis B infected patients were screened for Hepatitis D out of 11,190 patients where 1,444 found positive for Hepatitis D and 18% were due to missed screening of Hepatitis B (49).

ROLE OF HIGH-LOAD PERINATAL EXPOSURE IN HEPATITIS D INFECTION

Even though it is less common or rare as compared to other routes of transmission but may occur if the mother is infected with HBV. The transmission is primarily linked to exposure to contaminated blood during childbirth. Further lack of proper prenatal screening, lack of Hepatitis B preventative immunization in newborns and limited healthcare facilities increase the chances of transmission (50, 51).

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ROLE OF BEAUTY AND GROOMING SERVICE IN HEPATITIS D INFECTION

Weak infection control practices in grooming and beauty services (beauty salons) promote the indirect transmission of HDV infection by contributing to the spread of HBV which Hepatitis D is linked. The procedures such as, micro blading, shaving, manicures & pedicure, cosmetic treatments may cause the exposure with blood through infected tools and instruments (52). If the needles, grooming equipment and razors re-used & without appropriate sterilization or un following of infection prevention protocol. This way Hepatitis B infection transmitted from one client to another and thereby rise the risk for acquiring Hepatitis D (21, 53). Furthermore, lack of infection control guidelines, poorly trained staff and ineffective regulatory management lead to increase the risk for blood borne virus such as Hepatitis D transmission (54).

ROLE OF TRADITIONAL MEDICAL PRACTICE, NON- STERILE TATTOOING AND EAR- PIERCINGS IN HEPATITIS D INFECTION

Traditional medical practices can lead to the transmission of HDV in areas where infection-prevention measure is not properly followed practices such as scarification, traditional bloodletting and wet cupping break the skin and expose to blood. When the procedures are performed using unsterile instruments, they may facilitate Hepatitis B transmission as well as Hepatitis D virus (HDV) (3).

Getting tattoos in uncontrolled environments, shops that use non-sterilized needles, that punctures the dermis several times within a minute and infected tattoo ink act as vectors for the transmission of Hepatitis Virus including Hepatitis D virus (HDV) (55).

It is potentially high-risk pathway for HDV transmission, if piercing devices or guns which are contaminated with infected blood and reused without proper sterilization can lead the transmission of blood- borne infectious agent, along with HBV, thereby increasing risk of acquiring HDV (56).

DIAGNOSIS OF HEPATITIS D INFECTION

Accurate HDV diagnosis is important for timely disease management and reducing disease progression. However, the HDV diagnosis remains a multifaceted issue because the HDV depends on HBV for completing its life cycle and many infected people remain asymptomatic until disease progresses to complications (19, 23). Presently, the diagnosis of Hepatitis D virus (HDV) is based on a combination of molecular and serological identification. The initial serological identification can be performed through using CLIA or ELISA assay for qualitative detection (57-59). The molecular identification can be confirmed through performing qRT-PCR (quantitative real time polymerase chain reaction) which is recognized as gold standard method for confirmation of active virus (60, 61**).**

MANAGEMENT OF HEPATITIS D INFECTION

The management of Hepatitis D infection remains a major challenge in clinical hepatology, because HDV depends entirely on the host cellular machinery and HBsAg envelop for its virion assembly and transmission (62). According to current management guidelines from major international organizations such as (AASLD) American Association for the Study of Liver Disease, (EASL) European Association for the Study of the Liver and (WHO) World Health Organization, the main therapeutic objectives is to maintained suppression of Hepatitis D virus RNA, normalize the ALT level and prevent the progression of hepatocellular carcinoma and liver cirrhosis (63, 64).

Classically, off-label (Peg-IFN-α) PEGylated interferon Alfa represented the only finite therapeutic option which was prescribed for 48-72 weeks (65). However, its clinical applicability is widely limited by a high rate of post-therapy virological relapse and critical systemic adverse-effect profile that limit its use in individuals with decompensated hepatic disease (66). Although standard (NAs) nucleos(t)ide analogues such as entecavir or tenofovir are routinely used alongside to suppress active pre-existing Hepatitis B virus DNA replication because they don't show direct effect on Hepatitis D virus (HDV) RNA kinetics (67).

The global therapeutic field has undergone a primary paradigm shift through the identification of targeted, mechanism-based entry inhibitors and host-targeted agents. The entry blocking agents (BLV) Bulevirtide that specifically binds and blocks the hepatocytes receptor (NTCP) sodium taurocholate co-

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transporting polypeptide (13). Ultimately, for individuals who progress advanced hepatic failure due to chronic Hepatitis B and D co-infection then liver transplantation remains sole definitive treatment to improve survival and reduce the risk of mortality from end stage of hepatic disease (68, 69).

TREATMENT OF HEPATITIS D INFECTION

Hepatitis D infection is a preventable and advanced management are available but it is difficult to treat chronic HDV infection because HDV itself is an incomplete virus that requires helper virus (HBV) for its propagation. The major goals of treatment are to inhibit Hepatitis D virus (HDV) replication, mitigate liver inflammation, prevent the development of liver cirrhosis and HCC and improve clinical outcomes (70). Presently three types of antivirals are being used for Hepatitis D infection such as Pegylated Interferon Alfa, Bulevirtide and nucleos(t)ide analogues (2). Pegylated interferon alfa is the traditional antiviral therapy for chronic Hepatitis D infection use for 48 weeks. The peg-IFN-α works by the stimulation of immune response to HDV and suppressing the RNA of Hepatitis D virus (HDV) around 20 to 35% of treated individuals. However, therapeutic response varies significantly and after therapy relapse is common (71). The current treatment is being used is Bulevirtide which is an initial therapeutic agent for chronic HDV in many regions along with Europe. The mode of action of Pegylated Interferon Alfa is to inhibit virus entry into liver cell by blocking NTCP receptor on healthy liver cell. This treatment is for weeks, depends on the individuals clinical and virological response (72). Although, nucleos(t)ide analogous including, Tenofovir alafenamide, Entecavir and Tenofovir disoproxil fumarate use for chronic-infection of HBV-HDV. They work by inhibiting Hepatitis B replication (73).

PREVENTION AND CONTROL OF HEPATITIS D INFECTION

Prevention is the most effective intervention for reducing the spread of Hepatitis D infection. As the prevention of Hepatitis D virus (HDV) mainly depends on controlling of Hepatitis B virus (HBV) because there is no vaccine developed for HDV. However, the vaccination of HBV does not eradicate the Hepatitis D infection in people who are suffering from chronic Hepatitis B infection (47).

Hepatitis D virus (HDV) can be prevented through implementation of effective infection prevention procedures, and mitigation of recognized exposure risk factors, such as avoiding the exposure of infected blood, using sterile healthcare equipment and safe injection practice (14).

Further, community-based programs play significant role in reducing HBV and HDV transmission. They provide health awareness, encourage protective sexual behaviors, discourage the reusing of razors, needle, syringes and other items and improve harm reduction programs for intravenous drug users which help decrease the transmission of Hepatitis B and D (74).

In addition, appropriate clinical management and early diagnosis also promote Hepatitis D control. At present, the internal national guideline recommends regular Hepatitis D testing in all Hepatitis B-infected patients. Thus, the timely identification of HDV allows better monitoring, measurement of hepatic disease severity and timely starting of antiviral treatment when required which can reduce disease progression (75).

CONCLUSION

Hepatitis D infection is one of the highly aggressive types of viral hepatitis which is the causative agent HDV or delta virus and represents a major public health concern worldwide due to rapid disease advancement and adverse health outcomes. Where it increases the rate of mortality and morbidity. Since HDV is associated with HBV for completing it replication process. Moreover, several risk factors are responsible for the transmission of Hepatitis D infection, including unscreened blood transfusion, unsafe injection practice, non-sterile medical procedures and intravenous drug use. Timely the diagnosis of HDV through serological or molecular testing and early treatment is important for reducing the hepatic complication, liver failure and hepatic malignancy. Furthermore, the recent antiviral treatment has enhanced its management, although inadequate access to diagnostic facilities and treatment increase the risk of transmission. The promotion of HBV vaccination strategy, enhancing HDV screening in dialysis & OT

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procedures, which leads to public awareness & can decrease the Hepatitis D infection burden and improve quality of life.

Limitations of the study:

This review has several limitations that should be considered when interpreting its findings. First, it was conducted as a narrative review without a predefined systematic search protocol, such as the PRISMA guidelines; therefore, selection bias and the omission of relevant studies cannot be excluded. Second, epidemiological data on HDV from endemic regions, including Pakistan, Afghanistan, and Mongolia, remain limited and inconsistent, primarily due to the absence of routine screening and variable reporting practices. Third, the included studies differed in design, study population, diagnostic methodology, and case definitions, which restricts direct comparison and generalizability of the findings. Fourth, limited availability and lack of standardization of HDV RNA assays may have led to underestimation of the true disease burden. Fifth, evidence on emerging therapies, particularly bulevirtide, is derived largely from short-term studies, and data on long-term efficacy and safety remain insufficient. Future systematic reviews and multicenter studies are required to address these gaps and to strengthen the evidence base for HDV prevention and management in endemic settings.

Recommendations:

Preventive measures, early diagnosis, and appropriate treatment are necessary for the effective control and management of Hepatitis D Virus (HDV) infection. To prevent the spread of the virus, individuals in endemic areas should be vaccinated against Hepatitis B, refrain from sharing needles, and ensure the exclusive use of sterile medical equipment. Parenteral exposure concerns can be significantly reduced through the implementation of strict infection control procedures and comprehensive blood donor screening. It is also critical to raise public awareness regarding key risk factors and asymptomatic viral spread. Preventing severe hepatic complications and lowering the overall burden of disease can be achieved through prompt diagnostic identification and proper therapeutic management with recommended medications, such as pegylated interferon-alpha or entry-inhibitor therapies like bulevirtide.

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Conflict of interest:

Authors declared no conflict of interest.

Authors' contribution:

GA, RR & MKT Study design and data collection; GA, RR, MKT & AA Dietary assessment and statistical support; GA, AA, MBM & ARB Biochemical and laboratory analysis; GA, HT, SJ & SKP Fieldwork and participant management; GA, ARB & AA Critical analysis; RR & MKT Supervision and review.

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