

## REVIEW ARTICLE

# A Concise Review on Hepatitis C Virus Infection-Associated Type 2 Diabetes Mellitus and Its Impact on Anti-HCV Therapy

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*Received:* August 12, 2022; *Accepted:* September 21, 2022; *Published:* October 14, 2022 *DOI:* 10.36922/itps.v4i1.172

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## Abstract:

Hepatitis C virus (HCV), an RNA-containing virus, has infected more than 170 million people worldwide and is one of the leading causes of deaths in developing countries due to its propensity to progress to chronic states, followed by multiple fibrosis and scar formation (cirrhosis) and even hepatocellular carcinoma. Type 2 diabetes mellitus (T2DM), a metabolic disorder, is one of the diseases of civilization, and its prevalence has shown an increasing tendency globally. At present, more than 350 million people worldwide are suffering from T2DM. T2DM is considered the most common extrahepatic linkage of HCV infection, which is associated with prevalent morbidity and mortality patterns. Several studies have reported that HCV patients are more prone to developing T2DM as compared to healthy non-infected individuals. Extensive studies have revealed that HCV patients tend to develop insulin resistance (IR), which plays a crucial role in the development of T2DM. IR develops through several pathophysiological mechanisms, including the inhibition of insulin signaling pathway that induces central IR by HCV proteins and increased lipolysis as well as the overproduction of inflammatory cytokines, which promote peripheral IR. IR has a direct effect on the association of HCV with T2DM, and it has been found associated with impaired sustained virological response (SVR) and a higher incidence of hepatocellular carcinoma in HCV patients. Therefore, it has been suggested that chronic HCV patients must be treated with anti-HCV therapy along with antidiabetic medications to better achieve SVR. In this review, we briefly describe HCV infection, its diagnosis, global epidemiology, treatment options, and its association with DM, along with its impact on anti-HCV therapy.

**Keywords:** Comorbidity with diabetes mellitus, Hepatitis C virus infection, Insulin resistance, Management, Treatment

## 1. Introduction

Hepatitis refers to the inflammation of liver. The term “hepatitis” is a combination of two words: “Hepar,” which is a Greek word, meaning liver; and “-itis,” which is a Latin word, meaning inflammation.

Liver inflammation may be triggered by various factors, such as viruses, alcohol, autoimmune reactions, and drugs. However, hepatitis caused by viruses is responsible for many mortality and morbidity cases associated with liver disorders. These

viruses critically regulate the widespread prevalence of the disease [1,2]. Viral hepatitis is not caused by a single virus, but rather by various viruses, such as hepatitis A virus, hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis delta virus, and hepatitis E virus (HEV). HBV and HCV are the main culprit of hepatitis, and they are mostly associated with chronic fulminant hepatitis, cirrhosis, hepatic carcinoma, ascites, and mortality [3]. Hepatitis C, a blood-borne viral infection, may damage the liver if left untreated. It has been estimated that 3% (170–180 million

people) of the world's population are infected with HCV, in which 50–80% of individuals may develop chronic infection [4]. Hepatitis C is the leading cause of morbidity and mortality worldwide and is responsible for hepatocellular carcinoma and chronic liver disease [5].

Diabetes mellitus (DM), a metabolic disorder of immense public health importance, is becoming more prevalent. More than 420 million people are suffering from DM, and its prevalence is expected to rise to 629 million by the year 2045 [6]. Furthermore, it has also been estimated that about 318 million adults have impaired glucose tolerance, which marks a risk of developing DM in the near future [7]. Such patients have impaired glucose metabolism, but their blood sugar levels do not reach the cutoff value that is necessary for a diagnosis of DM [7,8].

Various studies have reported an association between HCV and DM and declared DM as the most common extrahepatic manifestation of HCV infection [7-10]. Several other extrahepatic manifestations such as porphyria cutanea tarda, glomerulonephritis, and cryoglobulinemia are also associated with HCV; however, Type 2 DM (T2DM) has been found to be potentially linked with HCV infection, attributing its excessive risk to direct viral immersion or secondary to HCV-induced fatal liver damage [11]. It is assumed that about one-third of HCV patients may have T2DM [12]. According to a meta-analysis, HCV-infected patients are more prone to developing T2DM as compared to non-infected patients, having an odd ratio of 1.68 and a 95% confidence interval of 1.15–2.45 [13]. Another meta-analysis reported similar results both, in retrospective and prospective studies [14]. It has also been reported that patients coinfecting with HCV and HIV had higher T2DM prevalence than those who were infected exclusively with HIV, having an odd ratio of 1.82 and a 95% confidence interval of 1.27–2.38 [15].

Several studies have revealed that HCV patients tend to develop insulin resistance (IR), which plays a crucial role in the development of T2DM. IR develops due to various pathophysiological mechanisms, including the inhibition of insulin signaling pathway that induces central IR by HCV proteins and increased lipolysis as well as the overproduction of inflammatory cytokines, which promote peripheral IR [16,17]. IR has a direct effect on the association of HCV with T2DM, and it

has been found associated with impaired sustained virological response (SVR) and a higher incidence of hepatocellular carcinoma in HCV patients [18].

The association between HCV and T2DM is of primary importance as a small increment of DM risk in HCV patients becomes a clinical concern considering the reduced effectiveness of available therapies for HCV in the presence of DM. Therefore, it has been suggested that chronic HCV patients must be treated with anti-HCV therapy along with antidiabetic medications to better achieve SVR [19].

In this review, we briefly describe HCV infection, its diagnosis, global epidemiology, treatment options, and its association with DM, along with its impact on anti-HCV therapy.

## 2. Hepatitis C

HCV infection is a major health concern worldwide. HCV, a ribonucleic acid (RNA)-containing virus, has infected a large number of people globally [3]. Hepatitis C infection is one of the leading causes of death in developing countries considering its propensity to progress to chronic states, followed by multiple fibrosis and scar formation (cirrhosis) as well as hepatocellular carcinoma [5]. Numerous studies have reported that the incubation period of HCV infection is 6–12 weeks. Hepatitis C infection can be asymptomatic or mild, but it progresses to a chronic state in up to 85% of patients. It takes 10–18 years from an acute infection to the development of chronic hepatitis [19]. Approximately more than 170 million people are infected by HCV globally. Once the virus enters the body percutaneously or parentally, it causes constant infection in the host. Although many remedies are used against HCV, its basic mechanism has not been identified. Almost 70–80% of cases of HCV become chronic with time, leading to cirrhosis, end-stage liver disease, and hepatocellular carcinoma. Coinfection of other disease along with HCV further worsens the liver condition. The condition of the liver is associated with immunosuppression. Comorbid conditions such as HCV and IR may aggravate liver fibrosis and result in less therapeutic response to therapy [20].

### 2.1. Types of hepatitis C

Hepatitis C infection can be classified into two groups based on symptoms: Acute hepatitis and chronic hepatitis.

### 2.1.1. Acute hepatitis C

HCV infection is said to be acute from the onset of infection up to 6 months. In majority of the cases (75–85%), the acute phase of HCV infection shows no signs and symptoms; only a small number of patients (15–25%) would show signs and symptoms of the disease [7]. The symptoms of acute hepatitis C tend to be generalized and non-specific; thus, they do not aid in the diagnosis of this disease. Some of the chief complaints associated with acute hepatitis C include jaundice, loss of appetite, abdominal discomfort, lethargy, flu-like symptoms, and itching [10].

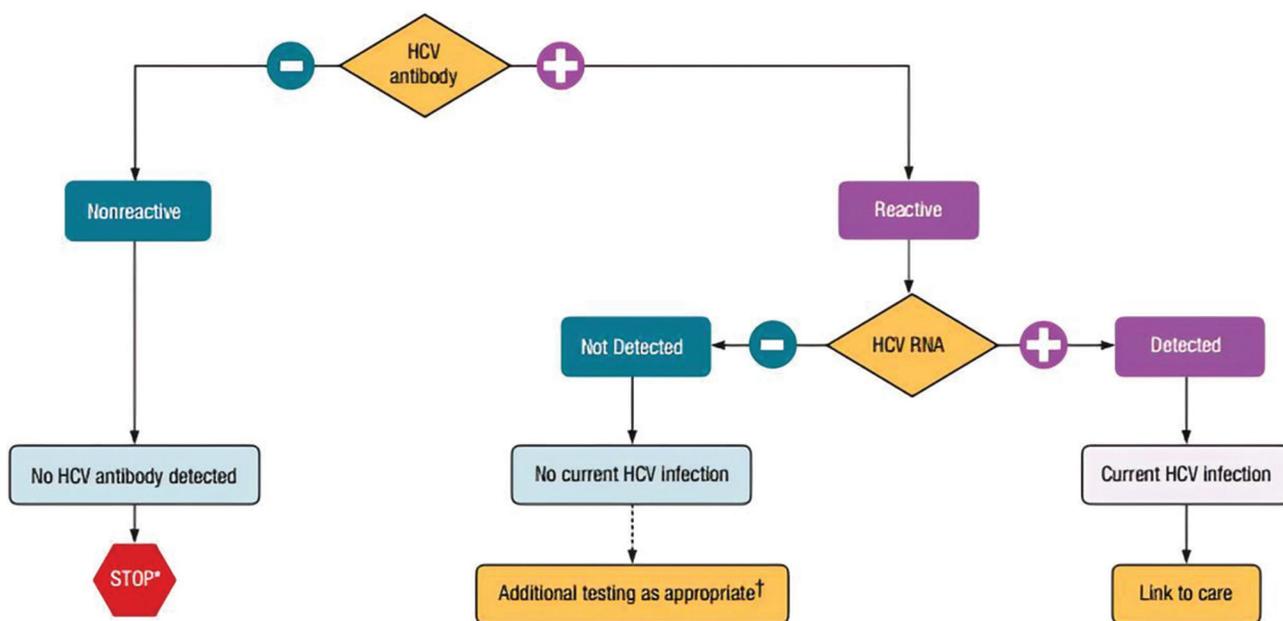
### 2.1.2. Chronic hepatitis C

When hepatitis C infection persists more than 6 months, then it is known as chronic hepatitis C. Chronic hepatitis C may remain asymptomatic during initial stages; its symptoms tend to appear in later stages [7]. Chronic hepatitis C is often diagnosed incidentally, and there is no fixed course of treatment, as it varies among individuals suffering from HCV [18]. Furthermore, fibrosis is known to develop in all chronic HCV carriers, but the rate of fibrosis varies among patients. A recent study reported that about one-third of chronic HCV patients who are not taking any medications developed

liver cirrhosis within 20 years, while the other one-third developed cirrhosis after 20 (20–30) years [15]. This process is affected by several factors, including sex (the progression rate in females is lower as compared to males), age (advanced age is associated with more rapid progression), alcohol use (higher progression rates among alcohol consumers), presence of fatty liver (the presence of fat in liver cells has been found associated with an increased rate of disease progression), and HIV coinfection (higher disease progression rate) [17].

### 2.2. Diagnosis of HCV infection

The main purpose of diagnosing a viral infection is to allow the infected person to be identified and treated. The diagnosis of viral infection is also important for preventing disease progression and viral transmission. The majority of primary HCV-infected patients remain asymptomatic; therefore, HCV infection cannot be diagnosed solely based on symptoms. HCV viremia (HCV in blood) could still exist despite normal serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Therefore, virological methods such as polymerase chain reaction (PCR) should also be used, rather than relying on serum ALT levels alone to diagnose HCV infection [18-21] (Figure 1).



**Figure 1.** HCV testing flowchart recommended by the Center for Disease Control (CDC). With copyright permission from the CDC.

### 2.2.1. HCV antibody testing

Serological methods such as detecting antibody against HCV are advisable for the diagnosis of HCV infection. The synthesis of antibodies against hepatitis C within the body can be detected in the blood after 2–3 months of the viral attack. Once the body is exposed to hepatitis virus, antibodies are formed against the virus. They are responsible for showing a positive test against the virus [20].

### 2.2.2. Enzyme-linked immunosorbent assay (ELISA) for antibody detection

Virological diagnosis of infection is based on the detection of anti-HCV antibodies by ELISA [5]. ELISA, a third-generation test for detecting HCV antibodies, is now commonly used in many diagnostic laboratories due to its high sensitivity of up to 98.90% and specificity of 100% in chronic liver disease patients with HCV [4,13]. ELISA is inexpensive and relatively easy to use for the diagnosis of HCV. Moreover, this technique could be fully automated and adapted to large testing volume. Therefore, the detection of HCV antibodies has been recommended for HCV infection screening by ELISA. However, this assay has some limitations; for instance, there is a possibility of reaction with maternal antibodies when used in infants younger than 18 months [8,14].

### 2.2.3. Detection of viral RNA

A molecular procedure known as nucleic acid test or nucleic acid amplification is used for the detection of certain pathogens, including virus or bacterium, in blood samples or any other body fluids or tissues. This test can be classified as signal amplification, probe amplification, and target amplification [22]. Reverse transcription PCR (Rt-PCR) is a target amplification method, which is used for the detection of HCV RNA. Similarly, signal amplification and transcription-mediated amplification methods are also used for this purpose [22,23]. The presence of HCV RNA in serum serves as a reliable marker of viremia (presence of virus in blood). An international standard for HCV quantification units, such as HCV RNA international unit (IU), has been established by the World Health Organization (WHO). This standard is used irrespective of which methods are used among all commercially available HCV RNA quantitative assays [22].

### 2.2.4. Qualitative HCV RNA detection

A qualitative test is often used to detect the presence or absence of HCV RNA in infected individuals. This test reports whether HCV RNA is present (positive) or non-detected (negative). An active infection is confirmed in patients who tested positive for ELISA by the use of qualitative assays [17].

Qualitative HCV RNA detection methods function based on the principle of target amplification, including transcription-mediated assay and real-time PCR. The Food and Drug Administration has approved several qualitative assays for the detection of HCV RNA [18].

### 2.2.5. Quantitative HCV RNA detection

PCR is a quantitative HCV RNA test used to measure the number of copies of HCV RNA, a genetic material of HCV in the blood, which is also termed as viral load. Viral load is used for monitoring patient's response toward anti-HCV therapies. Physicians would usually screen out the treatment options (i.e., anti-HCV therapies) by assessing the viral loads before, during, and after each treatment [18]. Rt-PCR is considered the method of choice for the quantification of HCV RNA level (viral load) in infected individuals [19]. This technique has wide dynamic range of quantification because of its high sensitivity and reduced chances of carryover contamination [24].

## 2.3. Genotypes of hepatitis C

There are six genotypes of hepatitis C, which can be further divided into their subtypes. The HCV genotypes are as follows:

- (i) Genotype 1 subtypes 1a and 1b
- (ii) Genotype 2 subtypes 2a, 2b, 2c, and 2d
- (iii) Genotype 3 subtypes 3a, 3b, 3c, 3d, 3e, and 3f
- (iv) Genotype 4 subtypes 4a, 4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i, and 4j
- (v) Genotype 5 subtype 5a
- (vi) Genotype 6 subtype 6a

Six major viral genotypes and over 50 proposed subtypes of HCV have been identified worldwide. The determination of viral genotype before treatment is now advised as a routine assay. Patients infected with genotypes 1 and 4 with viral loads higher than 800,000 IU/mL must be treated for

1 year, while those infected with other genotypes may be treated for only 6 months. Therefore, determining the genotype of HCV is important for the prognosis and follow-up of HCV-infected patients [25]. Genotypes 1 and 2 are more prevalent in West Africa and Europe, genotype 3 is more prevalent in South Asia, genotype 4 is prevalent in Central Africa and the Middle East, genotype 5 is more common in South Africa, while genotype 6 is more common in Southeast Asia [26].

#### **2.4. Treatment of hepatitis C infection**

If patients lack access to quality healthcare, improvements in diagnosing active hepatitis C and advancements in treatment would have insignificant effect on the morbidity and mortality associated with HCV. According to estimates, only 15–25% of Americans with chronic HCV infection receive treatment. Similarly, it has been estimated that only 15–25% of people with chronic HCV infection are receiving therapy on a global scale [23]. In fact, referrals to doctors who can and will evaluate these patients before treatment are often delayed or never made. Therefore, it is essential that all patients with active hepatitis C and positive HCV RNA are referred to and assessed by a health-care provider who is skilled in determining the degree of liver disease and in administering HCV treatment. Furthermore, patients who have DM or another disease as a comorbidity need to have their disorder managed specifically [24]. In a study, patients who received treatment were cured of their HCV infection and gained positive health effects, such as a reduction in liver inflammation, a decrease in fibrosis regression rate, and a 50% reduction in cirrhosis rate [24]. There is strong evidence showing that the coinfection and comorbidity of other diseases with HCV further worsen the liver condition. Immunosuppression is closely associated with the liver condition. Comorbid conditions like HCV with IR may aggravate liver fibrosis and result in less therapeutic response to therapy [27].

##### **2.4.1. Early treatment options**

After interferon was developed as an antiviral medication to treat HCV, subsequent milestones in the field of chemotherapy have been achieved. Interferon is the first and most widely used

medication to treat chronic hepatitis C. It is used both, on its own and in conjunction with other medications like ribavirin [20–22].

##### **2.4.2. Interferon**

Interferon is protein in nature, and its production is enhanced in the presence of any pathogens, such as protozoa, bacteria and their endotoxins, viruses, as well as intracellular parasites. Recombinant interferon is a purified sterile interferon product that can be administered subcutaneously or intramuscularly. The recommended course of treatment is 48 weeks in case of chronic HCV; however, it may be recommended for a shorter duration of time in patients whose serum HCV RNA levels are insignificant [12]. Recombinant interferon is produced by recombinant DNA technique from *Pseudomonas* cells that have genetically engineered plasmid. It is engineered with a gene of human leukocyte interferon. The resultant interferon has the same structure, pharmacology, and biological activity to that of human leukocyte interferon. Although interferon is considered safe, it may cause mild-to-moderate adverse reactions, including flu-like symptoms, headache, shivering, high-grade fever, fatigue, and myalgia. It is contraindicated in patients who have a history of hypersensitivity to interferon-alpha [15–18].

##### **2.4.3. Pegylated interferon**

Pegylated interferon, also termed as peg-interferon, was widely used against HCV infection as an early treatment option. It is a long-acting interferon, which is prepared from interferon and polyethylene glycol (PEG) through pegylation. It is indicated for chronic HCV-positive patients (both, cirrhotic and non-cirrhotic patients) with symptoms of liver inflammation and viral replication [7–9].

Peg-interferon is indicated in combination with ribavirin, an antiviral drug, in genotypes 2, 3, and 4 chronic HCV patients over 24 weeks, with the former being administered once a week. Nowadays, peg-interferon is also administered with direct-acting antiviral agents in almost all viral genotypes [10]. Although peg-interferon is considered safe, it is contraindicated in patients who have a previous history of hypersensitivity reaction to PEG, interferon-alpha, or other ingredients of the product [11].

#### 2.4.4. Ribavirin

Ribavirin, a nucleoside analogue, has well-known antiviral action against both, DNA and RNA viruses. It was administered with interferon and peg-interferon as early treatment options for HCV. It is currently administered with direct-acting antivirals (DAAs) in almost all HCV genotypes. Ribavirin has documented antiviral coverage, in which its efficacy has been recorded against 20 different types of RNA and DNA viruses *in vitro*. It stops the synthesis (production) of nucleic acid by acting on the target sites of cellular enzymes [15]. Ribavirin is recommended for a duration of 48 weeks in genotype 1 hepatitis C patients and for 24 weeks in genotypes 2 and 3 HCV patients [23].

### 2.5. Current treatment options

#### 2.5.1. DAAs

The previous conventional therapy available was of long duration with many disadvantages, including high cost, side effects, and resistance to therapy. Therefore, there has been an immense search for effective, inexpensive, non-toxic, and short duration therapies for HCV. Considering that HCV has the ability to mutate rapidly and develop resistance to antiviral drugs, which would result in immunosuppression, new antiviral agents are developed with the goals of decreasing viral load in the blood, lowering the risk of infectivity, reducing the intensity of inflammation and necrosis, prolonging the development of hepatic fibrosis and cirrhosis, as well as preventing the condition from progressing in severity, that is, preventing carcinoma [24-28].

DAAs are gaining popularity due to the fact that they can be used to treat HCV infection on their own. It has been reported by *in vivo* and *in vitro* studies that DAAs have the potential to challenge and weaken resistant viruses. They have the capability to cause a rapid first phase decrease in HCV RNA when used in combination with interferon. Using ribavirin with DAAs increases the second phase decline by increasing the clearance of virus from infected cells. DAAs comprise a group of drugs, which include boceprevir, telaprevir, simeprevir, faldaprevir, danoprevir, sovalprevir, asunaprevir, and sofosbuvir [17-19].

### 2.6. Global epidemiology of hepatitis C infection

Hepatitis C infection has a significant global impact. The WHO estimates that 150–170 million people worldwide (2–3% of the world's population) are infected with HCV. Many HCV-infected people are affected by hepatic cancer and cirrhosis. Every year, 350,000–450,000 people die from liver disorders associated with hepatitis C [4]. There are significant regional differences in terms of HCV prevalence; for instance, more than 10% of people in Egypt are infected with HCV according to the WHO, whereas the prevalence of HCV infection is significantly higher in Africa and Western specific areas compared to North America and Europe. According to the WHO, it has been reported that 15 million people in Europe are infected with HCV, of whom 2% are adults [27,28]. In the USA and Europe, chronic hepatitis C is the most common anomaly of the liver and the leading cause of liver transplant in these stated areas [29].

### 2.7. Hepatitis C comorbidities

Comorbidity refers to the occurrence of two disorders or illnesses in the same person concurrently or consecutively. Hence, when another disease or disorder occurs along with hepatitis C, this is known as HCV comorbidity. According to Leroy *et al.*, HCV-infected patients reported almost double the number of comorbidities compared to uninfected individuals [28]. Similarly, a study reported comorbidities in 13% of the HCV-infected population compared with 3.7% of the uninfected population [30].

The comorbidities related to chronic hepatitis C infection are associated with poor treatment outcomes. Therefore, these comorbidities should be carefully evaluated before the initiation of treatment and even during treatment itself [30]. There are multiple comorbidities associated with hepatitis C, including DM, HIV, HBV, hypertension, chronic kidney disease, cardiovascular disease, and depression [31].

#### 2.7.1. Hepatitis C with DM

Both HCV and DM (Type 2) are chronic diseases that have high mortality and morbidity worldwide. They are closely linked with each other. This association between HCV and DM was first

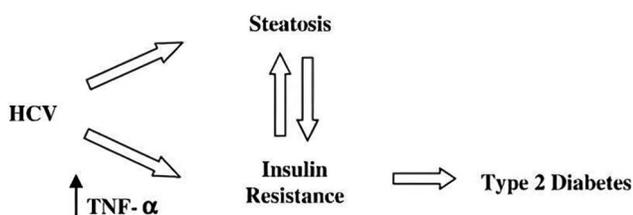
reported by Allison *et al.* in 1994 [31]. Recent epidemiological studies have reported that HCV infection influences the development of T2DM. Similarly, the frequency of DM (Type II) reported to be higher in HCV patients when compared with the normal population in European countries, suggesting an epidemiological connection between hepatitis C infection and T2DM [32].

The development of diabetes may also be influenced by HCV infection, as reported in a number of studies. In developed countries, the prevalence of T2DM (2% to 9.4%) in patients with HCV infection is higher than those with other types of chronic hepatitis. According to Naing *et al.*, HCV is a risk factor that increases the likelihood of developing DM [23]. The casual relation between HCV and DM has also been reported by Mehta *et al.* through a cross-sectional, general population-based study, indicating that HCV-associated T2DM is more prevalent among people aged 40 years or older [33].

### 2.7.2. Mechanism of association between hepatitis C and DM

Diabetes and IR may arise at any stage of HCV infection. There are many theories as to why people with chronic hepatitis C develop IR and diabetes. HCV primarily causes IR by interfering with the insulin signaling cascade in hepatocytes, triggering an inflammatory response by increasing the production of cytokines, such as tumor necrosis factor (TNF)-alpha and interleukin-6, as well as raising the levels of oxidative stress [34].

In chronic HCV infection, changes in hepatic lipid and glucose metabolism are commonly observed. About 50% of HCV-infected patients have hepatic steatosis (fatty liver disease), with HCV genotype 3 being primarily responsible [35]. IR occurs following steatosis triggered by HCV, and the proposed mechanism of steatosis-mediated IR is the accumulation of intracellular fats followed by DM [35,36] (Figure 2).



**Figure 2.** Mechanism of HCV-induced IR [35].

TNF, which is induced by HCV proteins, inhibits the activity of insulin receptor substrates (IRS) and lowers the expression of lipoprotein lipase and glucose transporter-4 (Glut-4) in peripheral organs. Reduced Glut-4 expression is linked to the development of IR and T2DM [35].

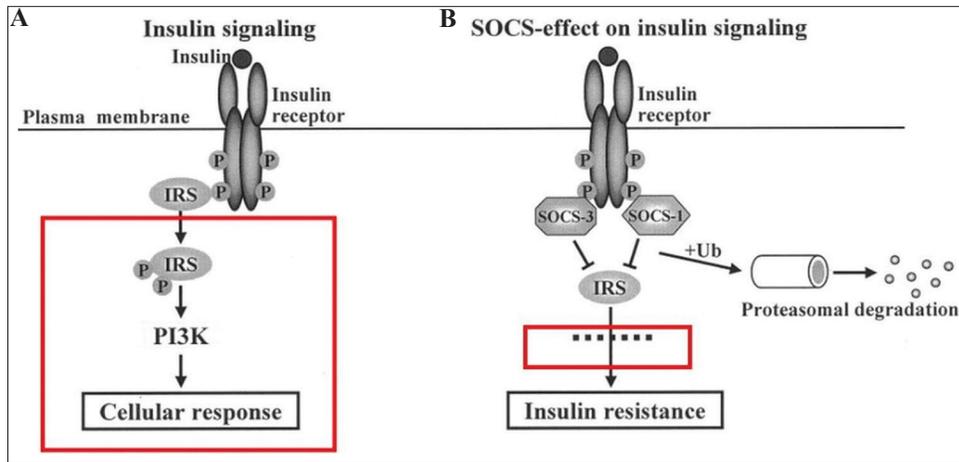
IR is induced by HCV non-genotype 3 through the downregulation of IRS. HCV genotype 3 may, however, affect pancreatic beta cells in a cytopathic (pathological alterations in cells) manner and through autoimmune aggressiveness, which may result in IR. In addition, HCV may also cause liver hepatocyte necrosis, which, in turn, leads to the malfunction of insulin receptors [35]. The association between HCV and IR has also been demonstrated in HCV patients having high IR compared to uninfected controls. It has been proposed that HCV centrally targets phosphatidylinositol-3-kinase (PI3K)-protein kinase B (Akt/PKB) signaling pathway, whose phosphorylation is impaired on insulin stimulation [35-37].

### 2.8. Impact of DM on anti-HCV therapy

There is reduced response to interferon (INF) and ribavirin combination therapy in HCV patients with IR and T2DM. This reduction in response to anti-HCV therapy may be partly induced by PI3K pathway, which blocks the translocation of signal transducer and activator of transcription 1 (STAT1) into the nucleus following activation by insulin [36-38] (Figure 3).

IR and T2DM are important disease modifiers in patients with chronic hepatitis C. These characteristics lead to various adverse treatment outcomes in HCV patients, including increased liver fibrosis, decreased end-of-treatment virological response (ETVR) and SVR rates, the emergence of hepatocellular carcinoma (HCC), and some cardiovascular events like stroke [36-39]. When regimens containing DAAs, such as sofosbuvir, telaprevir, boceprevir, and danoprevir, are used, the negative association between IR and virological response is either mitigated or disappears. It is possible that the virological response to the next IFN-free regimens would not be affected by IR [35,36].

IR caused by HCV may lead to T2DM in some patients in addition to fibrosis, HCC, and a poor response to IFN therapy. Furthermore, the effectiveness of anti-HCV therapy may be



**Figure 3.** Mechanism of cellular response and insulin resistance [36]. The red boxes indicate the induction of cellular response and insulin resistance.

impaired by hepatic steatosis, most likely because hyperinsulinemia diminishes the therapeutic effect of interferon [37,38]. The increased protein tyrosine phosphatase (PTP) levels, which prevent the phosphorylation of the STAT pathway, are likewise mediated by IR. The suppression of the STAT signaling pathway reduces the efficiency of IFN therapy and lowers the SVR rate by inactivating a number of essential transcription factors in the interferon signaling cascades [39].

### 3. Recommendations

To rule out HCV infection in diabetic populations, it is crucial to monitor and take early preventative measures for T2DM. Therefore, if patients with HCV positivity and advanced age are responding poorly or not at all to anti-viral medications, blood glucose testing is advisable. Before commencing anti-HCV therapy, IR should be improved, so as to ensure that patients would respond well to medication. Lifestyle changes and the use of insulin sensitizers like metformin to reduce hepatic gluconeogenesis as well as pioglitazone to activate insulin receptors and remove visceral fat to subcutaneous tissues are all recommended for HCV patients to prevent weight gain. To acquire the best outcomes from the therapy, more attention and specific goals are required for this specific population (HCV+DM). In addition, it is important to provide prescribed medications in accordance with international standards (uniform central control). Hence, there is a need for further studies and policy development in this area.

### 4. Conclusion

DM and hepatitis C infection are chronic conditions that are common and prevalent around the world. This review comes to the conclusion that there is a strong two-way relationship between T2DM and HCV infection. In the presence of one disease, the other disease is highly affected. Diabetes worsens hepatitis C outcomes and increases the risk of developing HCC and liver cirrhosis, while hepatitis C infection causes DM, particularly T2DM. This review also concludes that HCV-positive patients show a poor response to antiviral therapy with the presence of T2DM.

### Acknowledgments

None.

### Funding

None.

### Conflict of interest

There are no conflicts of interest among the authors.

### Author contributions

All authors have contributed equally to this work.

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

## Availability of data

Not applicable.

## Further disclosure

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