Hepatitis C and Atherosclerosis: Inflammatory Interplay

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Abstract

Atherosclerosis along with viral hepatitis C are major health problems. Despite the fact that atherosclerosis is usually associated only with blood vessels, and hepatitis C with the liver, these diseases have a number of common features. The pathogenesis of atherosclerosis includes many different mechanisms, one of the central roles among which is inflammation. The importance of inflammation for the development of hepatitis is also difficult to overestimate. The precise mechanisms of action by which HCV stimulates development of atherosclerosis are still being investigated. Both direct and indirect consequences of HCV infection, such as persistent inflammation and impairments in glucose and lipid metabolism, are well known atherogenic conditions. In this review, we have tried to describe the interaction between hepatitis C and atherosclerosis, with a particular focus on inflammation.

Keywords: Atherosclerosis; Hepatitis C; HCV; Liver disease.

Significance | A review of relationship between HCV infection, inflammation, and cardiovascular pathologies.

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Pathophysiology of Atherosclerosis

There is a number of traditionally recognized risk factors for atherosclerosis, such as higher low-density lipoprotein cholesterol (LDL-C) or decreased high-density lipoprotein cholesterol (HDL-C) concentrations in blood, smoking, diabetes mellitus (DM), high blood pressure, insufficient physical activity, unhealthy eating habits, and psychosocial distress (Haberal et al., 2020). These factors can negatively affect vascular tone regulation, coagulation and inflammatory response pathways. Atherosclerosis is a chronic condition that includes several stages. It starts with endothelial dysfunction which allows blood cholesterol to invade the vessel walls. This triggers a chain of inflammatory pathways involving immune cells such as macrophages, dendritic cells and leukocytes that migrate to the vascular wall. As a result, a lipid layer is being formed in the artery which can develop to a plaque over time (Rafieian-Kopaei et al., 2014).

Atherosclerosis is usually asymptomatic in earlier stages and is often identified during imaging tests carried out for other purposes. The clinical manifestation becomes apparent at a stage when the coronary artery lumen is narrowed significantly (generally >70%) or if there is an acute plaque rupture (Lusis, 2000). Atherosclerotic plaque erosion sets off a platelet reaction that can lead to a thrombus formation in the vessel. The thrombus can block the blood flow in the vessel and the myocardium supplied by it partially or completely which frequently results in cardiovascular incidents such as cerebral vascular accident, acute

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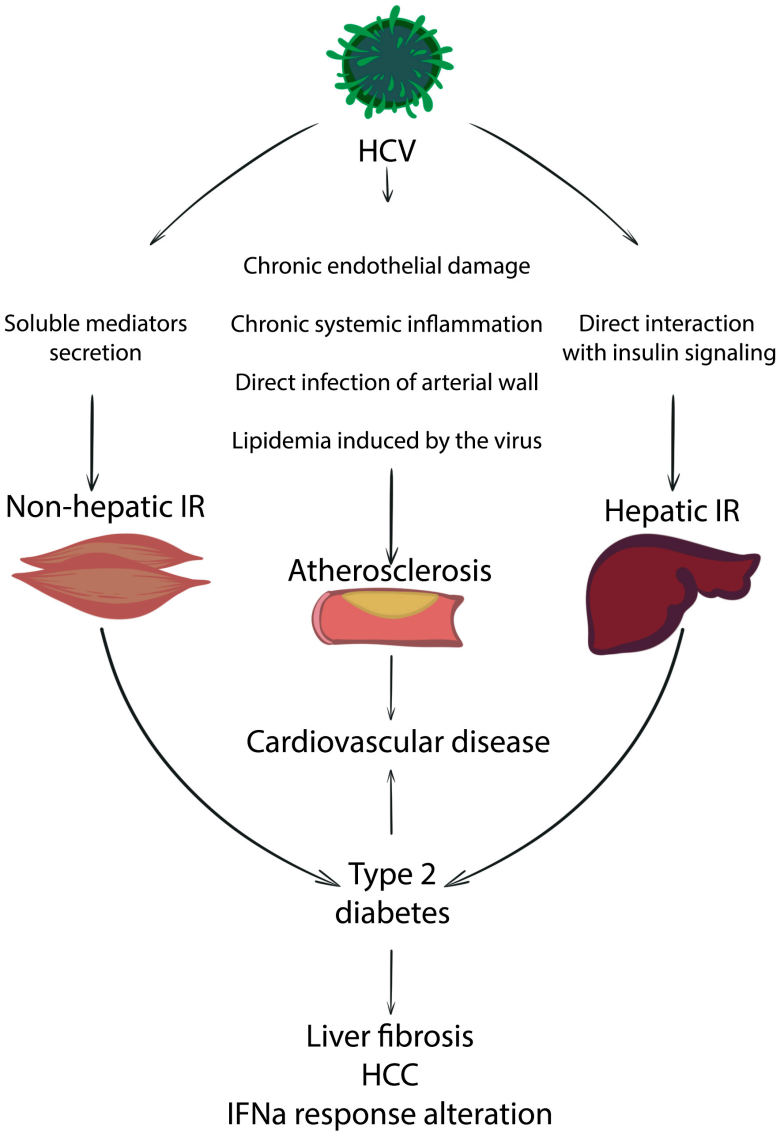

Figure 1. Interactions between HCV-induced actions.
HCV plays a crucial role in T2DM, atherosclerosis and other disease conditions. The most recent ACC/AHA Guideline on the Management of Blood Cholesterol has recognized that patients with chronic inflammatory conditions (HIV, rheumatoid arthritis and psoriasis in particular) have greater risk for atherosclerotic CVD and that these disorders should be considered as risk factors when discussing ASCVD prevention.

coronary syndrome or peripheral arterial disease (Asada et al., 2020).

Atherosclerosis and Inflammation

Controlling cholesterol concentrations in blood is an established way of diminishing atherosclerotic complications. However, inflammation is also an important risk factor. Several studies have shown that inflammatory cells, primarily monocytes and macrophages, mediate the atherosclerotic process. Mononuclear phagocytes tether to activated endothelium via leukocyte adhesion molecules (Kang et al., 2021). Cytokines then stimulate monocyte migration into the artery wall after which the monocytes differentiate into macrophages, multiply and promote artery wall transformation. Lipoproteins, specifically lipoprotein- associated phospholipase A2 (Lp-PLA2) created by macrophages, adds to the inflammatory response. The enzyme hydrolyzes oxidized phospholipids in LDL and sends inflammatory signals. Lp-PLA2 is frequently present in the necrotic core of atherosclerotic lesions (Lorey et al., 2022).

Chronic inflammatory disorders, such as lupus, rheumatoid and psoriatic arthritis, diabetes, and end-stage renal failure, increase the risk of atherosclerosis and consequential cardiovascular diseases (Arida et al., 2018). The studies have shown that anti-inflammatory drugs, specifically methotrexate and colchicine, reduce the cardiovascular risk significantly, presumably by inhibiting the inflammatory response (Ma and Chen, 2021). However, their mechanism of action is still being studied. The most recent ACC/AHA Guideline on the Management of Blood Cholesterol has recognized that patients with chronic inflammatory conditions (HIV, rheumatoid arthritis and psoriasis in particular) have greater risk for atherosclerotic CVD and that these disorders should be considered as risk factors when discussing ASCVD prevention (Grundy et al., 2019). In Figure 1, we summarized the scheme of the interaction between various of HCV-induced actions, which leads to T2DM, atherosclerosis, and other conditions.

Hepatitis C virus

According to the World Health Organization, 130 to 170 million people worldwide are infected with Hepatitis C virus (HCV) which makes it a major cause of liver disorders. Around 10% to 20% of chronic hepatitis C (CHC) patients suffer from persistent liver inflammation resulting in liver cirrhosis and hepatocellular carcinoma on later stages (Lee et al., 2014). Extrahepatic symptoms include autoimmune diseases, disorders of glucose and lipid metabolism, atherogenic dyslipidemia, lymphoproliferative disorders, mixed cryoglobulinemic disease, kidney dysfunction, impaired insulin sensitivity (IR), type 2 diabetes (T2DM), Sjögren's syndrome, and rheumatoid arthritis-like polyarthritis. In addition, over 50% of chronically infected patients develop metabolic bone disease and osteopenia (Lei et al., 2019). The metabolic manifestations are mainly caused by disruptions of glucose and lipid homeostasis due to HCV infection. IR and DM are observed more frequently in the course of the infection and after liver transplantation in chronically infected subjects, independent of the stage of liver fibrosis. The number of HCV-infected subjects is higher among individuals with diabetes compared with the age-matched general population (Kralj et al., 2016). HCV causes systemic and liver inflammation that elevates the atherosclerotic risk because of increased levels of pro-inflammatory cytokines and chemokines. There has also been reported a correlation between atherosclerosis and high serum adiponectin/tumor necrosis factor alpha (TNF-α) related to IR in subjects infected with HCV (Babiker et al., 2020).

HCV infection not only damages the liver directly, but also sets off a series of metabolic impairments (primarily in glucose and lipid homeostasis) which contribute to hepatic dysfunction and stimulate the development of extrahepatic consequences. This is why best clinical practice requires a thorough research of the disease's metabolic effect on the human body in order to find optimal treatment strategies (Chang, 2016).

Hepatitis C and atherosclerosis

Trials

The association between HCV infection and atherosclerosis was first reported by Ishizaka et al. after two larger studies carried out in 2002 (Ishizaka et al., 2002) and 2003 (Ishizaka et al., 2003) among subjects in the general population (Ishizaka et al., 2014). Both studies showed that HCV-infected patients had greater risk of atherosclerosis independent of the presence of other atherogenic risk factors. Another study assessing a large number of individuals from the general population in Japan, reported greater arterial stiffness in subjects with HCV infection compared to control group that was HCV-negative (Tomiyama et al., 2003). These findings were confirmed by Fukui et al. in a cohort of subjects with T2DM (Fukui et al., 2003). The study showed that patients who presented positivity to anti-HCV antibodies had greater risk of both plaque and higher carotid intima-media-thickness (CIMT) irrespective of other risk factors. This correlation was further confirmed by two studies carried out by Boddi et al. (Boddi et al., 2007) and Targher et al. (Targher et al., 2007) in Italy. Both studies showed that the prevalence of increased CIMT was significantly higher in HCV-infected individuals than in controls, which proves anti-HCV positivity to be an independent risk factor of increased CIMT.

Another study performed on a large cohort of Egyptian individuals compared the prevalence of atherosclerosis in patients with HCV infection, HCV subjects with viral clearance, and controls (individuals never infected). While there was reported no difference in prevalence of atherosclerosis between subjects with active and those with past infection, HCV-infected individuals

demonstrated greater risk of atherosclerosis after adjustment for other established CVD risk factors (Mostafa et al., 2010).

Petta et al. assessed CA in a group of biopsy-identified CHC genotype 1 subjects. The reported prevalence of atherosclerosis in HCV subjects was 41.9% while the corresponding rate among control subjects was much lower at 22.9%. Furthermore, the study showed an independent correlation between the severity of liver fibrosis and the risk of plaques (Petta et al., 2012).

In a recent study (Adinolfi et al., 2012), atherosclerosis was evaluated in a large group of consecutive biopsy-proven CHC subjects with and without steatosis. HCV subjects demonstrated significantly higher prevalence of CA compared to HCV-negative controls (53.7% and 34.3%, respectively, $P < 0.0001$). HCV subjects without the presence of steatosis revealed a much higher prevalence of CA than controls without steatosis (26.0% vs 14.8%, $P < 0.015$) while HCV subjects with steatosis showed a much higher prevalence of CA than subjects with non-alcoholic fatty liver disease (77.7% vs 57.8%, $P < 0.0001$). These findings prove the causal effect of HCV in development of atherosclerosis and that individuals with HCV-induced steatosis showed the highest prevalence of CA independent of HCV genotype, gender, age, and severity of liver damage. In addition, multivariate analysis showed that HCV-induced steatosis is an independent predictor of CA with an AUC of 0.78 (95%CI: 0.71-0.85, $P < 0.0001$; with a positive specificity of 81.7% and sensitivity of 74.2%). These results provide evidence that steatosis mediates atherosclerosis already in early stages and thus can be deemed a good marker of higher atherosclerotic risk in patients. HCV-induced steatosis is associated with such pro-atherogenic factors as metabolic dysfunctions, IR, hyper-homocysteinaemia, hepatic inflammation and fibrosis, hypo-adiponectinaemia and TNF-α, and oxidative stress (OXS). Such data suggest that steatosis contributes to the development of atherosclerosis by stimulating inflammatory processes and metabolic disruptions. Moreover, the study revealed atherosclerosis in 34% of HCV subjects below 50 years old and plaques in 24.1% of the subjects. The corresponding rates for HCV-negative controls were significantly lower: 16% and 3.9% correspondingly. These results prove that HCV infection is a predisposing factor for early development of atherosclerosis and severe carotid changes irrespective of a more favourable CVD risk factor profile with lower plasma cholesterol concentrations and lower metabolic syndrome prevalence.

HIV-infected subjects also revealed a higher risk of CA. A study carried out by Sosner et al. revealed a higher prevalence of carotid plaque in subjects co-infected with HIV and HCV which again proves the independent effect of HCV infection in the development of atherosclerosis (Sosner et al., 2012).

However, a number of other studies did not find any association between HCV infection and CA in contrast to the data mentioned above. Bilora et al. (Bilora et al., 2008) and Caliskan et al.(Caliskan et al., 2009), for instance, did not confirm such an association in a cohort of hemodialysis subjects. Likewise, Tien et al. (Tien et al., 2009) in the setting of HCV-positive women with and without HIV co-infection, did not reveal any association between HCV infection and atherosclerosis following an adjustment for confounding factors. Neither could a strict association between HCV infection and CA be confirmed by Masiá et al. (Masiá et al., 2011) in a cohort of HIV co-infected subjects.

It is worth mentioning that the majority of studies that did confirm the association between HCV infection and CA, involved a larger number of patients, while the studies that did not show any association, were carried out on small groups of either hemodialysed or HCV/HIV co-infected subjects (Goodkin et al., 2017). Since CA is a multifactorial disease, false negative results could be generated in studies with lower statistical power, which means that their medical significance can be questioned. The contradiction among the studies can be explained by a number of factors such as variation among the involved patient cohorts, difference in HCV infection evaluation, severity of liver damage in patients, atherosclerosis assessment methods and, most importantly, adjustment for confounding factors and comparator control groups. All in all, the analysis of available studies strengthens the notion that HCV infection is an independent risk factor for CA. However, there is still a need for more prospective studies and meta-analytic assessments in order to gain a more accurate understanding of how HCV influences the development of atherosclerosis.

Mechanisms

Longer exposure to inflammatory cytokines also activates the endothelium that expresses adhesion molecules, resulting in an atherogenic state mediated by immune cells. Several studies assessing this relationship have revealed a higher risk of cardiovascular incidents and heart failure in HCV-infected subjects (Soehnlein and Libby, 2021). A study among patients with stable coronary heart disease revealed increased levels of TNF-α (7.1 vs. 4.8; $P < 0.01$), but decreased C-reactive protein level (2.6 vs. 4.4; $P < 0.01$) in HCV-infected subjects, as well as significantly higher prevalence of cardiovascular events and heart failure (HR = 2.13; 95% CI: 1.19-3.80) (Tsui et al., 2009).

Another cross-sectional study that assessed atherosclerosis by measuring the CIMT, observed that CHC patients demonstrate higher prevalence of atherosclerosis than non-infected subjects (Roed et al., 2014). Furthermore, irrespective of viral presence in serum, atherosclerotic plaques in arteries contained isolated HCV RNA sequences, which proves the causal role of HCV in development of inflammation-induced atherosclerotic plaques.

The precise mechanisms of action by which HCV stimulates development of atherosclerosis are still being investigated. Both direct and indirect consequences of HCV infection, such as persistent inflammation and impairments in glucose and lipid metabolism, are well known atherogenic conditions. A study comparing CIMT in successfully treated patients and in infected and untreated subjects revealed that HCV clearance decreased the CIMT significantly (from 0.94 mm to 0.81 mm, $P < 0.001$) (Iorga et al., 2020). However, it did not affect the already existing plaques which indicates the importance of early treatment.

A pioneer Japanese study by Ishizaka et al. reported an association between HCV infection and atherosclerosis (Ishizaka et al., 2002, Ishizaka et al., 2003). Several independent studies confirmed this view, the prevalence of carotid plaques being revealed in 38% to 64% of HCV-infected subjects (Voulgaris and Sevastianos, 2016). Furthermore, HCV infection can be deemed an independent risk factor for increased CIMT. In contrast, several smaller studies could not prove such a strict association. It is worth mentioning that these were low power studies conducted in small cohorts of hemodialysis or HCV-infected subjects and their clinical significance can thus be questioned. The most recent meta-analytic reviews confirmed the existence of such an association. Based on the data, HCV infection triggers several pathophysiological mechanisms that contribute to the development of atherosclerosis (Lee et al., 2019).

Persistent inflammation is a well-known independent risk factor for the development of plaque and the atherogenic effect of HCV infection is largely due to chronic inflammation caused by the infection. CHC patients demonstrate increased levels of IL-6 and TNFα, INF, and IL-2 concentrations as well as higher levels of pro- and anti-inflammatory cytokines (Zampino et al., 2013). Inflammatory cytokines induced by the infection lead to an atherogenic state by up-regulating intracellular adhesion molecules, expression of antibodies in endothelium, and OXS. The chain of inflammatory reactions progresses during the course of the infection and the formation of fibrosis. Furthermore, pro-fibrogenic pathways induced by the infection, seem to contribute to the formation and consolidation of plaques. A recent study has again proved the role of inflammation in HCV-induced atherosclerosis (Kany et al., 2019). The study estimated the inflammation by measuring Galectin-3-binding protein (Gal-3BP) levels in a cohort of HCV-infected women compared to control subjects. Gal-3BP is a marker of M1 macrophages that are most likely to stimulate the inflammatory process and plaque rupture (Hanna et al., 2017). The study showed a significant association between the prevalence of inflammatory markers and CAD in the HCV infection setting.

Another inflammation-causing mechanism in HCV infection involves platelet- activating factor (PAF), a potent phospholipid activator and inflammation mediator. This mechanism was described in a study of HCV-induced vascular damage (Ashraf and Nookala, 2023). PAF is hydrolyzed by plasma PAF-acetyl-hydrolase (pPAF-AH), an enzyme that is usually linked to LDL and HDL in human plasma as the lipoproteins support its activity (Campo et al., 2008). HCV is also associated with plasma lipoproteins. HCV-infected subjects demonstrated a severe decrease in pPAF-AH activity and as a result showed higher PAF levels. The pPAF-AH activity returned back to normal only in subjects that underwent a successful anti-HCV treatment and showed a sustained virologic response (SVR) (Sidorkiewicz, 2021). These data suggest that HCV infection affects the PAF/pPAF-AH balance which contributes to the inflammatory process and increases the vascular damage.

HCV also increases the levels of oxidized low-density lipoprotein (oxLDL) which is directly involved in the development of CA. The combination of such factors as hepatic inflammation, OXS and the following expression of increased oxLDL levels constitutes the pathophysiological association between HCV infection, oxLDL and the development of atherosclerosis (Solbach et al., 2015). Studies also reported the presence of isolated HCV RNA strands in plaque tissue which indicates an active local infection.

Finally, HCV infection is associated with a number of well-known pro-atherogenic factors, such as IR and DMT2 which contributes to the pathophysiological effect on CA development. IR triggers a series of broad toxic effects, such as disorders of glucose and lipid metabolism, increased blood pressure, higher inflammatory tone, elevated levels of advanced glycosylation end products, and pro-oxidative state (Wang et al., 2022). Consequently, subjects with HCV-induced IR may be at higher risk for the development of atherosclerotic plaques.

Association of HCV with other cardiovascular conditions

Coronary heart disease

Several studies that evaluated the association between atherosclerosis and HCV infection have shown conflicting results. Although the majority of studies in a systematic review reported a probability of a higher risk for coronary heart disease (CHD) among HCV-infected subjects, their clinical significance is doubtful (Babiker et al., 2017). There has been a significant variation in terms of methods and results. Other studies reported the same results. Forde et al. did not reveal any difference in the prevalence of CHD among HCV-infected subjects compared to non-infected control groups, as well as with regard to coronary revascularization. However, the studies reporting no association between HCV infection and CHD included some subjects after a spontaneous clearance of HCV infection which may have affected the results (Forde et al., 2012).

Few studies assessing CHD events differentiate RNA positivity and HCV antibody. A larger study reported a higher prevalence of

CHD events in subjects with HCV seropositivity compared with control groups (4.9% vs 3.2%). The data suggests that HCV seropositivity is an independent risk factor for CHD. Furthermore, patients with HCV-RNA positivity exhibited a significantly higher prevalence of CHD events compared with individuals only with HCV antibody (5.9% vs 4.7%). The incidence of CHD events was thus higher in HCV seropositive subjects of whom the incidence was greatest among individuals with detectable HCV-RNA compared to those who were only antibody-positive (Pothineni et al., 2014). One of the clinical manifestations of CVD is electrocardiogram (ECG) changes. HCV infection also correlates with a greater risk of an ischemic-appearing ECG compared with non-infected individuals which suggests a possible association between HCV seropositivity and an ischemic ECG (Lin et al., 2014). Butt et al. (Butt et al., 2009) found out that HCV-infected patients demonstrated decreased lipid levels and lower incidence of hypertension compared to non-HCV individuals. Following adjustment for other established risk factors, HCV infection showed an association with an increased risk for CHD incidents, despite a more favourable cardiovascular risk profile. These findings have been confirmed in another study involving a group of diabetic patients (Hsu et al., 2014). The study was performed on three cohorts: subjects treated with pegylated interferon in combination with ribavirin, untreated HCV-matched patients and an uninfected cohort of diabetic subjects without HCV. The study showed that the ischemic stroke and CHD prevalence was lowest in HCV subjects who received the peginterferon and ribavirin treatment compared with the non-infected diabetic cohort and the untreated HCV-infected cohort. It is worth mentioning that the incidences of ischemic stroke and CHD in treated subjects with peripheral artery disease (PAD) were not reduced. These data shows that the negative cardiovascular effect of HCV can be eliminated at earlier stages, while at advanced stages of atherosclerosis the anti-HCV treatment cannot attenuate the cardiovascular damage.

Peripheral artery disease

PAD is a frequent underdiagnosed and undertreated disorder. Some studies show that HCV may be associated with PAD prevalence. One retrospective study involved 7641 HCV-positive subjects and 30564 matched controls. The study showed higher risk of PAD in HCV-infected subjects compared with HCV-negative individuals. Higher PAD prevalence in HCV-infected subjects was observed within the first year. The study reported no correlation between gender and risk for PAD development, however, aging did have such an effect. The study did not take such factors as cigarette smoking, level of physical activity or obesity into consideration (Hsu et al., 2015).

Cardiovascular mortality

Considering the atherogenic effect of HCV infection, many studies have estimated its correlation with CVD-related mortality in parallel with other viral infections. In a retrospective study by Guiltinan et al. (Guiltinan et al., 2008) HCV antibody-positive and HCV antibody-negative subjects matched for gender and age were involved. The study showed a significantly higher overall mortality rate in HCV-infected subjects, including prevalent mortality from hepatic disorders and CVD. The REVEAL study (Lee et al., 2012) performed on a cohort of 1095 anti-CHV-positive subjects and 760 patients with detectable HCV RNA, showed that the CVD-related mortality was greater among patients that were anti-HCV-positive compared with seronegative individuals.

Direct-acting antiviral therapy and cardiovascular disease

In a 2017 study Daiber et al. recognized endothelial dysfunction as the main consequence of cardiovascular disorder (Daiber et al., 2017). A prospective study performed by Petta et al. (Petta et al., 2017), assessed the correlation between SVR and the CA levels in subjects with progressive hepatic fibrosis or liver cirrhosis. The results revealed a CIMT decrease in subjects on DAA treatment after 9-12 months of follow up after viral elimination. Flow-mediated dilation (FMD), a recognized cardiovascular risk marker, is a well-known accurate and non-invasive method of measuring the endothelial function. Di Minno et al. reported that FMD increased from 4.52% at baseline to 9.39% following the DAA treatment (Di Minno et al., 2020). Positive FMD alteration after 12 weeks following DAA therapy has been confirmed in later trials. These data prove the correlation between eradication of the virus and improvement of endothelial function.

A number of large multicenter research trials proved the connection between DAA-related SVR and a decrease in cardiovascular incidents. A study performed by Butt et al. (Butt et al., 2019) among 12,667 CHC subjects showed a 43% reduction in the risk of cardiovascular incidents in patients treated with DAA, compared with a 22% reduction in subjects treated with pegylated interferon and ribavirin. Main limitations of this study include heterogeneity of the cohort primarily consisting of male subjects (96,1%), the trial's retrospective nature and implementation of ICD-9-CM/ICD-10 codes for endpoints. A recent prospective study conducted by Adinolfi et al. on a cohort of 2,204 HCV subjects (Adinolfi et al., 2020), revealed a 2.0–3.5-fold decrease in cardiovascular events (including stroke, acute coronary syndrome, or TIA) after DAA-induced HCV eradication and a 0.68% decrease in the annual incidence of CV risk. The results were not affected by pre-treatment severity of liver fibrosis.

DAA therapy shows positive effect on CVD events and at the same time has a benign cardiovascular safety profile. An Egyptian study by Biomy et al. (Biomy et al., 2017) did not report any arrhythmias in HCV-infected patients with and without liver cirrhosis after

DAAs treatment. The study estimated DAAs impact on CVD adverse events in 170 HCV patients and did not reveal any changes in QTc interval. A more recent Egyptian study confirmed these results. Furthermore, according to McGlynn et al. (McGlynn et al., 2019), there was not indicated any association between the use of DAAs and risk for hepatic or renal complications or more frequent hospitalizations. The research provides strong evidence that hepatitis C virus is an independent, yet not traditionally recognized risk factor for cardiovascular disorders. According to the abovementioned studies, DAA-induced SVR may decrease the risk for CVD. Moreover, viral eradication after DAA treatment leads to considerable improvement of endothelial function in CHC patients. The data suggest that DAA therapy may decrease the prevalence of cardiovascular incidents in CHC patients. However, further research is required in order to assess the long-term impact of that.

Discussion

Our review focused on examining the relationship between HCV infection and cardiovascular pathologies, with a particular emphasis on the role of inflammation in linking hepatitis C to atherosclerosis. Atherosclerosis serves as a fundamental process underlying the development of various cardiovascular diseases. While studies have presented conflicting results, the connection between both diseases and inflammation remains undeniable.

The complex pathogenesis of atherosclerosis suggests a multifaceted interaction at different levels. For instance, it has been observed that prolonged exposure to inflammatory cytokines triggers the activation of endothelial cells, leading to the expression of adhesion molecules and subsequently creating an atherogenic state mediated by immune cells.

However, despite the existing knowledge, further research and testing are still imperative. The implementation of additional studies will not only uncover potential similarities and relationships in the pathogenesis of these two significant diseases but also enhance the efficacy of treatment and the safety of therapeutic strategies. Moreover, it will expand the range of potential drugs available for managing these conditions.

In conclusion, the association between HCV infection and cardiovascular pathologies, particularly through the inflammation-mediated link to atherosclerosis, necessitates continued investigation. Advancements in this field have the potential to deepen our comprehension of the development of these diseases and open doors to more effective treatment options and expanded therapeutic approaches.

Conclusion

In our review, we considered data on the relationship between HCV infection and cardiovascular pathologies. We paid a precise attention to the inflammation, which links hepatitis C to the atherosclerosis. Atherosclerosis, in turn, underlies almost all cardiovascular diseases. Studies have shown conflicting results, but the association of both diseases with inflammation is undeniable. The complex pathogenesis of atherosclerosis suggests an interaction at different levels. For example, it has been shown that longer exposure to inflammatory cytokines also activates the endothelium that expresses adhesion molecules, resulting in an atherogenic state mediated by immune cells. To date, it is clear that further research and testing is needed. Their implementation will reveal similarities and relationships in the development of two serious diseases, as well as increase the effectiveness of their treatment, the safety of the therapeutic strategies used, and expand the possible range of drugs.

Author Contributions

A.V.P. wrote, and drafted; V.N.S., L.V.N., E.M.P., A.A.M., A.N.O. wrote, reviewed and edited the article.

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Competing financial interests

The authors have no conflict of interest.

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