Other Extrahepatic Manifestations of Hepatitis C Virus Infection (Pulmonary, Idiopathic Thrombocytopenic Purpura, Nondiabetes Endocrine Disorders)

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KEYWORDS

• Hepatitis C • Extrahepatic manifestations • Pulmonary • Endocrine
• Idiopathic thrombocytopenic purpura

KEY POINTS

- Hepatitis C Virus (HCV) infection may increase the risk for obstructive, interstitial, and vascular lung disease, lung cancer, and mortality in HCV-infected lung transplant recipients.
- HCV infection may increase the risk of idiopathic thrombocytopenic purpura, nonresponse to corticosteroids during the treatment, and higher rates of splenectomy.
- HCV infection may increase the risk of autoimmune thyroiditis, infertility, growth hormone and adrenal deficiency, osteoporosis, and low-trauma fractures.
- Targeted prospective cohorts may confirm these results mostly obtained from small case-control studies with different study populations and low level of evidence.

INTRODUCTION

Hepatitis C virus (HCV) is a widespread infection with an estimated prevalence of at least 1.8% in the American population and is a leading cause of liver-related morbidity and mortality worldwide.[1] In addition to hepatocytes, it also infects, and replicates in, extrahepatic tissues and peripheral mononuclear blood cells.[2,3] Therefore, it is not surprising that HCV infection is also associated with extrahepatic manifestations evolving

Disclosure Statement: The authors have nothing to disclose.

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Clin Liver Dis ■ (2017) ■–■
http://dx.doi.org/10.1016/j.cld.2017.03.014 liver.theclinics.com

simultaneously with, or independent from, viral hepatitis, cirrhosis, portal hypertension, or hepatocellular cancer. The prevalence of extrahepatic manifestations in HCV infection largely depends on the definition of this condition, but seems to concern up to 0.9% to 1.4% of 16,761 HCV-infected patients identified in various high-risk groups in Lazio, Italy.[4]

In this review, we summarize the current evidence for potential pulmonary and non-diabetic endocrine extrahepatic manifestations of HCV.

Pulmonary Manifestations of Hepatitis C Virus Infection

There is accumulating evidence on a potential interaction between HCV virus infection and pulmonary extrahepatic manifestations (**Table 1**). These range from potentially increased rates of obstructive and restrictive pneumopathies, as well as malignant and autoimmune manifestations. In addition to HCV-induced cirrhosis and/or portal hypertension, lung health seems to be influenced directly by HCV through changes to immune response by an alteration in T lymphocytes, eosinophilic granulocytes, and inflammatory cytokines, which may account for interstitial or alveolar inflammation and a higher rate of obstructive lung disease and lung fibrosis.[5–7]

Lung function and obstructive lung diseases

There are controversial data on the relationship between HCV infection and lung function. Cross-sectional analyses from the Third National Health and Nutrition Examination Survey among 9159 patients suggest an increase in forced expiratory volume in 1 second (FEV_1) and full vital capacity in anti-HCV antibody–positive versus –negative subjects; however, these associations were no longer significant after additional adjustment for cocaine and marijuana use as well as poverty income ratio.[8] Another cross-sectional study on the prevalence of HCV infection among patients with chronic obstructive pulmonary disease found a notably increased prevalence of HCV infection (7.5%; 95% confidence interval [CI], 6.52–8.48) in comparison with blood donors as a control group (0.41%; 95% CI, 0.40–0.42). In contrast with the aforementioned study, HCV-positive patients showed a significantly lower FEV_1 than HCV-negative patients ($34.7 \pm 8.6\%$ vs $42.7 \pm 16.5\%$).[9] However, these results may be due to a generally more advanced chronic obstructive pulmonary disease stage, leading to a significant selection bias. A small prospective cohort study among 59 patients assessed the decline in FEV_1 and diffusing capacity of the lung for carbon monoxide in current smokers and ex-smokers, which were significantly higher in HCV-positive patients than in HCV-negative patients.[10] The same study group interestingly detected an increased impaired reversibility with salbutamol among asthmatic HCV patients with no response to interferon therapy.[11]

Nevertheless, these results could not be confirmed in a cross-sectional analysis among 1068 human immunodeficiency virus (HIV)-infected individuals with no evidence of an independent association between markers of HCV exposure, chronicity, viremia, or HCV-associated end-organ damage with obstructive lung disease.[12] Whether HCV infection leads to a faster decline in lung function and to a potentially higher prevalence of obstructive lung disease still needs to be verified in large, prospective cohort studies in the general population.

Pulmonary hypertension

The role of HCV in the development, progression and improvement of pulmonary hypertension (PH), independent from or simultaneously with liver cirrhosis and portal hypertension, is not well-understood.

Table 1
Pulmonary manifestations of HCV infection

Authors	Design	Study Population	Results/Conclusion
Lung function/obstructive lung diseases			
Fischer et al,[12] 2014	Cross-sectional study	1068 participants with intravenous drug use from the Acquired Immunodeficiency Syndrome Linked to the Intravenous Experience Study	No independent association between markers of HCV exposure, chronicity, viremia, or HCV-associated end-organ damage with obstructive lung disease.
Kanazawa & Yoshikawa,[11] 2004	Prospective cohort study	55 HCV-positive patients with asthma undergoing IFN treatment vs HCV-negative patients (matched for age, sex, and baseline pulmonary function)	Nonresponders to IFN therapy with chronic HCV infection showed a significantly accelerated decline in lung function and impaired reversibility with salbutamol compared with IFN responders and HCV-negative controls.
Kanazawa et al,[10] 2003	Prospective cohort study	59 COPD patients	Chronic HCV infection might accelerate decline in lung function (FEV_1, DLCO) in patients with preexisting COPD.
Goh et al,[8] 2014	Cross-sectional study	9159 participants from a population-based cohort (NHANES III)	Exposure to HCV was significantly associated with an increase in FEV_1 and functional vital capacity. These associations were no longer significant after additionally adjusting for cocaine and marijuana use as well as poverty income ratio.
Silva et al,[9] 2010	Cross-sectional study	184 patients with COPD vs 16,138 blood donors	COPD patients showed a significantly higher prevalence of HCV infection than blood donors (OR, 29.2; 95% CI, 17.3–49.2; $P<.01$). HCV-positive patients had a significantly lower FEV_1 than the control group ($P = .01$).
Kubo et al,[6] 1996	Case-control study	13 patients with chronic HCV vs 13 healthy controls	Lavage lymphocyte and eosinophil numbers were increased in patients with HCV, but not total cell count. Surface marker analysis of the lymphocyte populations showed increases in CD2, CD3, CD4, and HLA-DR, but no difference in CD4/CD8 ratio.

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Authors	Design	Study Population	Results/Conclusion
PH			
Chen et al,[13] 2013	Cross-sectional study	100 cirrhotic patients	Cirrhotic patients with PPH had more frequently a history of HCV infection (20.0 vs 1.1%, $P = .03$) than those without PPH. However, HCV infection was not significantly associated with PPH in backward stepwise regression models.
Demir & Demir,[15] 2014	Case-control study	50 HCV-infected patients vs 50 healthy controls (prevalence of cirrhosis not reported)	HCV infection was significantly associated with right ventricular systolic dysfunction and PH (higher systolic pulmonary artery pressure and pulmonary vascular resistance, all $P<.01$) compared with healthy controls.
Sangal et al,[14] 2014	Cross-sectional study within a retrospective cohort	68 noncirrhotic patients with HIV–HCV coinfection	The prevalence of echocardiographic PH was higher (26%) in HIV–HCV coinfected individuals than the previously reported prevalence in HIV monoinfection (0.5%). IFN-based HCV treatment and time since HCV diagnosis were associated with the development of PH as assessed by echocardiography.
Renard et al,[16] 2016	Case series	3 cirrhotic patients (2 with HIV coinfection, 1 with PH)	Three cases of newly diagnosed or exacerbated pulmonary arterial hypertension in patients treated with sofosbuvir.
Lung transplantation			
Koenig et al,[17] 2016	Retrospective cohort study	17,762 lung transplant recipients from the Scientific Registry of Transplant Recipients (1994–2011) in the United States	In multivariate survival analysis, HCV infection was associated with higher mortality in lung transplant recipients (aHR, 1.24; 95% CI, 1.04–1.46; $P = .01$), whereas there was no association of HCV infection with time to graft loss.
Doucette et al,[18] 2016	Retrospective cohort study	14 HCV-positive vs 456 HCV-negative lung transplant recipients from the University of Alberta Lung Transplant Program (1986–2011)	1-, 3-, and 5-y survival rates were similar in HCV-positive and HCV-negative recipients.

Englum et al,[19] 2016	Retrospective cohort study	16,604 lung recipients from the United Network for Organ Sharing database (1994–2011)	Overall survival was shorter in the HCV-positive compared with HCV-negative donor group (median 1.3 vs 5.1 y; *P*<.01). Results were confirmed in adjusted analyses.
Lung cancer			
Allison et al,[20] 2015	Retrospective analysis of different cohorts/ registries	12,126 chronic HCV-infected persons from the Chronic Hepatitis Cohort Study vs 133,795,010 records from 13 cancer registries	HCV infection was associated with an increased for lung cancer compared with noninfected peers (standardized relative risk, 1.6; 95% CI, 1.3–1.9).
PE			
Ambrosino et al,[21] 2016	Systematic review and metaanalysis of case-control and retrospective cohort studies	VTE analysis: 100,364 HCV-infected patients vs 8,470,176 controls PE analysis: 100,254 HCV-infected patients vs 8,470,055 controls	HCV-infected subjects may exhibit an increased risk of VTE (OR, 1.88; 95% CI, 1.33–2.65, *P*<.01) with a nonsignificant trend toward an increased risk of PE compared with healthy controls (OR, 1.81; 95% CI, 0.90–3.66; *P* = .09).
Pulmonary fibrosis			
Ueda et al,[23] 1992	Case-control study	66 IPF patients vs 9464 age-matched controls	Prevalence of HCV infection was significantly higher in IPF patients than in healthy controls (28.8% vs 3.7%, *P*<.05).
Arase et al,[25] 2008	Case-control study	6150 HCV-infected patients vs 2050 HBV-infected patients (age and sex-matched)	Cumulative incidence rate of IPF after 20 y was significantly higher in HCV- than in HBV-infected patients (0.9% vs 0.0%, *P* = .02).
Irving et al,[24] 1993	Cross-sectional study	62 IPF patients	None of 62 IFP patients suffered from HCV infection; therefore. no increased prevalence of HCV infection compared with the general population.
Pulmonary sarcoidosis			
Goldberg et al,[26] 2006	Case reports, systematic literature review	667 HCV-infected patients treated with recombinant alpha-IFN vs 3862 IFN-naïve HCV patients	3 cases of biopsy-proven sarcoidosis in recombinant alpha-IFN recipients vs none in therapy- naïve patients (incidence rate 0.4% vs 0.0%, *P*<.01).

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Authors	Design	Study Population	Results/Conclusion
Ramos-Casals et al,[27] 2005	Case reports, systematic literature review	68 HCV-infected patients with incident sarcoidosis (20 treated with alpha-IFN monotherapy, 30 treated with alpha-IFN and ribavirin, 18 therapy-naïve patients)	In HCV infection, sarcoidosis may either be triggered by antiviral therapy (in 75% of cases) or occur spontaneously. Of 18 treatment-naïve HCV patients with sarcoidosis, 14 (87%) suffered from pulmonary involvement.
Faurie et al,[28] 2010	Case series from retrospective cohort study	11 patients with chronic HCV infection and sarcoidosis, partly obtained from a retrospective cohort of 3194 patients with chronic HCV infection	Sarcoidosis triggered by antiviral therapy was more frequent after completion of therapy and presented a benign outcome. In treatment-naïve HCV patients, systemic corticosteroids had to be used more often and outcome was less favorable.
Tuberculosis			
Wu et al,[31] 2015	Case-cohort analysis from a prospective population-based cohort	5454 HCV-infected vs 54,274 noninfected Taiwanese patients	HCV infection was significantly associated with active tuberculosis disease in multivariate Cox regression (aHR, 3.20; 95% CI, 1.85–5.53; $P<.01$) and competing death risk event analysis (aHR, 2.11; 95% CI, 1.39–3.20; $P<.01$).
Richards et al,[32] 2006	Cross-sectional study	272 hospitalized patients with tuberculosis in Georgia	Of 272 patients with tuberculosis, 61 (22.4%) were seropositive for HCV infection.
El-Serag et al,[33] 2003	Case-control study	34,204 HCV-infected patients vs 136,816 uninfected controls	HCV-infected patients showed a significantly higher prevalence of tuberculosis vs controls (3.3% vs 1.3%; $P<.01$), with similar results after exclusion of immunocompromised patients.

Lomtadze et al,[34] 2013	Prospective cohort study	326 patients with culture-confirmed tuberculosis and serial ALAT/ASAT measurements	In multivariable analysis, HCV coinfection was found to be an independent risk factor for incident antituberculosis drug-induced hepatotoxicity (aHR, 3.2; 95% CI, 1.6–6.5; *P*<.01).
Liu et al,[35] 2014	Retrospective cohort study	553 patients with active tuberculosis	Incidence of transient liver function impairment was significantly increased in patients with HCV than in controls (12% [20/161] vs 2% [9/392]; *P*<.01). However, mean onset times of drug-induced hepatotoxicity were not significantly different.

Abbreviations: aHR, adjusted hazard ratio; ALAT, alanine aminotransaminase; anti-Hbc, antibody against hepatitis B core protein; ASAT, aspartate aminotransaminase; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IFN, interferon; IPF, idiopathic pulmonary fibrosis; NHANES III, Third National Health and Nutrition Examination Survey; OR, odds ratio; PE, pulmonary embolism; PH, pulmonary hypertension; PPH, portopulmonary hypertension; VTE, venous thromboembolism.

Portopulmonary hypertension (PPH), a pulmonary vasoconstriction and vascular remodeling after chronic portal hypertension, is a rare condition. Chen and colleagues[13] conducted a small, cross-sectional study among 100 hospitalized cirrhotic patients. Ten patients presented with PPH, 8 with a viral etiology of their cirrhosis. The results showed a significantly higher rate of HCV infection compared with the control group without PPH (20.0% vs 1.1%, respectively; $P = .03$). However, HCV was not shown to be an independent risk factor for PPH.[13] Interestingly, another cross-sectional analysis among 68 noncirrhotic HIV–HCV coinfected patients reported a comparable high prevalence of PH/right heart dysfunction of 26%, as determined by transthoracic echocardiography. Despite the missing control group, the authors compared it with a generally lower frequency of 0.5% among HIV-monoinfected patients from other studies. Moreover, treatment with interferon, but not ribavirin, was significantly associated with PH (odds ratio [OR], 5.65; 95% CI, 1.07–29.93; $P = .04$).[14]

Another case-control study among 50 HCV-infected versus noninfected patients detected a significantly increased rate of right heart dysfunction and PH based on different hemodynamic markers measured by transthoracic echocardiography[15]; however, there was no information on concomitant portal hypertension and cirrhosis.

Curiously, a case series of 3 cirrhotic HCV-infected patients treated with sofosbuvir and ribavirin showed a newly diagnosed pulmonary arterial hypertension in 2 cases after completion of antiviral therapy with sustained virologic response, and a worsening of a preexisting pulmonary arterial hypertension in 1 patient about 2 months after start of treatment. The authors hypothesized that a decrease in vasodilatory inflammatory mediators after or during antiviral therapy may result in a clinical progression of pulmonary arterial hypertension.[16] However, 2 of those patients had HIV coinfection, whereas 1 suffered from portal hypertension, which may be potential confounders.

The role of HCV infection as an independent risk factor for PH merits further investigation. Similarly, PH as a potential adverse event of current antiviral therapy strategies may be studied further on.

Lung transplantation

In the field of lung transplantation, there are rather heterogeneous data on the role of HCV infection in mortality and transplant survival among both recipients and donors. A large prospective cohort study of 17,762 lung transplant recipients from the American Scientific Registry of Transplant Recipients found a significant association between HCV infection and greater overall mortality with an adjusted hazard ratio of 1.24 (95% CI, 1.04–1.46; $P = .01$). This was especially true for long-term mortality 3 years after transplantation, whereas the first 2 years did not show different death rates in HCV-positive versus HCV-negative individuals.[17] On the basis of these data, treatment of HCV infection in lung transplant recipients may result in a longer posttransplant survival. Another small case-control study, however, found no different 1-, 3-, and 5-year survival rates between HCV-positive versus HCV-negative recipients.[18] Changing the perspective, transplantation of HCV-positive donor lungs was shown to be associated with a poorer survival (median, 1.3 vs 5.1 years; $P<.01$) in their recipients compared with HCV-negative donor organs. Conversely, HCV infection in recipients did not significantly impact survival.[19]

Lung cancer

HCV infection has been hypothesized to be associated with a higher incidence rate of extrahepatic cancer. Among 12,126 chronic HCV-infected persons in the Chronic Hepatitis Cohort Study,[20] the risk of developing lung cancer was significantly increased with a standardized rate ratio of 1.6 (95% CI, 1.3–1.9). Further studies

may verify these results and investigate the potential mechanisms linking these 2 conditions.

Pulmonary embolism

The relationship between HCV infection and the risk of pulmonary embolism remains debatable. Recently, Ambrosino and colleagues[21] conducted a systematic literature search and meta-analysis of retrospective cohort, case-control and cross-sectional studies identifying an increased risk of deep vein thrombosis (6 studies, OR: 1.92; 95% CI, 1.35–2.72; $P<.01$); however, this was not confirmed in pulmonary embolism, with a trend toward an increased risk in this population (4 studies: OR, 1.81; 95% CI, 0.90–3.66). Because the number of participants was considerably high for the latter analysis, a power issue is rather improbable. However, because the studies were cross-sectional or retrospective and considerably varied in study design, an association between HCV can neither be reliably confirmed nor discarded.

Pulmonary fibrosis

There is some, however contradictive, literature on a possible association between HCV infection and idiopathic pulmonary fibrosis (IPF). A systematic literature review by Aliannejad and Ghanei[22] suggested that a higher frequency of HCV markers in IPF patients,[23] an increase in lymphocyte and neutrophil numbers in bronchoalveolar lavage of chronic HCV patients, and the development of IPF in interferon-treated HCV patients may predispose for pulmonary fibrosis. Whereas a small Japanese case-control study found a significantly increased prevalence of HCV seropositivity among 66 IPF patients compared with 9464 age-matched controls (28.8% vs 3.7%, respectively; $P<.05$),[23] these results could not be confirmed in a subsequent analysis of IPF patients in the United Kingdom.[24]

Conversely, HCV infection was significantly associated with incident IPF in a retrospective analysis of 6150 HCV-infected versus 2050 HBV-infected Japanese patients,[25] which may indicate an HCV-specific role in the development of lung fibrosis.

Pulmonary sarcoidosis

The role of HCV infection in extrahepatic sarcoidosis is not completely understood. In a case-control study, Goldberg and colleagues[26] reported 3 cases of histologically proven sarcoidosis with pulmonary involvement among HCV-infected patients treated with recombinant interferon-alpha, whereas no event was recorded in the interferon-naïve control group. However, there was also evidence of sarcoidosis in therapy-naïve HCV patients in a systematic review and retrospective case series,[27] including patients with HCV infections with 87% of pulmonary involvement. Interestingly, a different degree of aggressiveness of disease and steroid requirement was discussed for these 2 groups. For instance, a series of 11 cases with chronic HCV infection and histologically confirmed sarcoidosis from a retrospective French cohort study indicated systemic corticosteroids had to be used more often and outcome was less favorable in treatment-naïve patients[28] compared with those receiving interferon.

In a case report of a patient with chronic therapy-naïve HCV infection,[29] treatment with pegylated interferon-alpha and ribavirin for 48 weeks led to a complete clinical and histologic remission of symptoms, which corroborates the hypothesis of a direct virologic effect on the development and clinical course of this disease. As in other autoimmune and hematooncologic extrahepatic manifestations of HCV, a dysregulation of the cytokine/chemokine network may predispose for granulomatous diseases.[30] In light of the revolutionary changes in HCV therapy, examining the effect of new antiviral agents in the reversibility of sarcoidosis may warrant further investigation.

Tuberculosis

As shown in previous studies, HCV infection and tuberculosis share the comparable high-risk population with a high rate of HIV coinfection and socially difficult circumstances, such as homelessness and imprisonment.[31] Richards and colleagues[32] found a surprisingly high prevalence of 22.4% HCV coinfection among hospitalized patients with tuberculosis in Georgia. Conversely, in a case-control study among American veterans, there was an increased prevalence of tuberculosis coinfection in HCV-infected cases compared with noninfected controls,[33] however, to a lesser extent. These data were drawn from selected study samples, which may not represent the general population. However, a population-based, nationwide case-cohort study in Taiwan recently found a significantly increased risk of developing active tuberculosis in HCV-infected patients compared with age- and sex-matched peers the general population in Taiwan.[31] This strengthens the hypothesis of a shared cooccurrence owing to currently unknown mechanisms. However, a direct alteration of immune response to HCV seropositivity may exert a certain impact on the vulnerability to developing tuberculosis.

Despite a considerable hepatotoxicity of most antituberculosis drugs, little is known about the implication of HCV coinfection. In a prospective cohort study from Georgia including 326 patients with culture-confirmed tuberculosis, HCV coinfection resulted to be an independent risk factor for incident antituberculosis drug-induced hepatotoxicity as determined by monthly measured alanine aminotransferase levels during follow-up with an almost 3-fold risk increase compared with monoinfected peers and a faster development of liver injury after onset of antituberculosis therapy.[34] Likewise, a retrospective cohort study among 553 Taiwanese patients with active tuberculosis showed a higher rate of transient liver function impairment during antituberculosis treatment among HCV-infected patients.[35]

Once the controversy on the effect of HCV coinfection will be solved, it may be worthwhile to investigate the interactions of current antiviral and antituberculosis therapy in case of simultaneous occurrence.

Idiopathic Thrombocytopenic Purpura in Hepatitis C Virus–Infected Patients

Idiopathic thrombocytopenic purpura (ITP) is characterized by the destruction of thrombocytes in the spleen with the appearance of cutaneous and mucosal petechiae, epistaxis, menorrhagia, eventually causing major bleedings such as intracerebral hemorrhages (**Table 2**). Although the pathogenetic mechanisms are not completely understood, an alteration of immune response with formation of autoantibodies or cytotoxic T-lymphocytes directed against thrombocytic surface proteins as well as a suppressed platelet production may play a major role.[36] As potential triggering factors, especially viral infections,[37,38] lymphoproliferative and autoimmune diseases are discussed.[39,40] HCV may enhance autoimmune responses leading to thrombocytopenia by means of molecular mimicry[41] of platelet surface proteins and production of correspondent antibodies. Aref and colleagues investigated the most likely surface antigens in 50 HCV-infected patients (30 with thrombocytopenia) by flow cytometry and quantitative monoclonal immobilization of platelet antibodies. The most frequent platelet membrane glycoproteins (GP) were GP IIb/IIIa, GP IIIa, GP IIb, GP Ib, and GP Ia.[41,42] Moreover, HCV infection was associated with a significant elevation of platelet-associated immunoglobulin G compared with HBV-infected or healthy controls in a cross-sectional study among 421 patients with chronic hepatitis.[43]

In the 1990s, a cross-sectional study among 300 patients with lymphoproliferative or autoimmune diseases found a statistically significant correlation between HCV prevalence and number of autoimmune alterations in both conditions, suggesting

Table 2
ITP in HCV-infected patients

Authors	Design	Study Population	Results/Conclusion
Chiao et al,[37] 2009	Retrospective case-cohort study	120,908 American veterans with HCV	HCV was associated with elevated risk for ITP (HR, 1.8; 95% CI, 1.4–2.3) and overall incidence rates of ITP were higher compared with HCV-negative participants (30.2 vs 18.5 per 100,000 person-years). ITP incidence was increased among both untreated and treated HCV-infected persons.
Pivetti et al,[40] 1996	Cross-sectional study	300 patients with autoimmune disorders, thereof 33 patients with ITP and 167 with lymphoid malignancies	Statistically significant correlation between HCV prevalence and number of autoimmune alterations in both lymphoproliferative and connective tissue disorders, which was not found for anti-HBc positive patients. HCV may skew the immune system toward the production of autoantibodies.
Pockros et al,[44] 2002	Retrospective chart review	7 cases of ITP in 3440 patients with chronic HCV infection	ITP occurs more commonly in patients with chronic HCV infection than expected by chance.
Rajan et al,[45] 2005	Retrospective cohort study	250 patients with chronic thrombocytopenia	HCV patients (30%) had less severe thrombocytopenia. Symptoms and signs of thrombocytopenia were less frequent in HCV patients, but major bleeding was more frequent (25% vs 10%; $P<.01$).
Aref et al,[42] 2009	Cross-sectional study	50 patients with HCV	Platelet-specific antibodies in 86.7% of HCV patients. Target antigens for platelets antibodies: GP IIb/IIIa (30%), GP IIIa (20.5%), GP IIb (13.3%), GP Ib (13.3%), GP Ia (10%). Platelets count was inversely correlated with the levels of platelet GP-specific antibodies ($r = -0.42$, $P = .02$), and significantly parallel to spleen size ($P = .02$).
Sakuraya et al,[46] 2002	Prospective cohort study	79 patients with chronic ITP	HCV-infected patients with ITP required more often prednisolone treatment and splenectomy, but response rate to prednisolone treatment was significantly lower, as compared with noninfected controls (all $P<.01$).

Abbreviations: anti-Hbc, antibody against hepatitis B core protein; CI, confidence interval; GP, glycoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; ITP, idiopathic thrombocytopenic purpura.

that ITP may be potentially linked with HCV infection.[40] In a cohort of 3440 newly diagnosed HCV-infected patients, 7 developed ITP with 6 of 7 positive for anti-GP IIb/IIIA antibodies. Furthermore, the occurrence of ITP was significantly increased compared with data from the general population, which corroborated the hypothesis of an increased risk of ITP in HCV patients.[44]

In a large, retrospective analysis of HCV-infected US veterans compared with HCV-negative individuals matched by age, gender, visit date, and outpatient/inpatient consultation, HCV-infection was associated with an increased risk for ITP (HR, 1.8%; 95% CI, 1.4–2.3), which was true for both untreated and treated patients.[37] In a retrospective cohort study among 250 patients with chronic thrombocytopenia, those with exclusively noncirrhotic HCV infection exhibited fewer symptoms of thrombocytopenia, such as bruising, petechiae, and mucosal bleeding, but higher rates of major bleeding compared with HCV-seronegative peers,[45] so that the authors discuss HCV-mediated idiopathic thrombocytopenia as a different entity from other etiologies.

Whereas an association between HCV infection and ITP is probable, there is little evidence investigating its impact on ITP treatment. Sakuraya and colleagues[46] found a significantly higher rate of prednisolone therapy and splenectomy, and lower response rate to corticosteroids in HCV-infected patients compared with seronegative controls. Conversely, ITP as a potential serious adverse event during or even after interferon treatment in HCV patients has been described in some case reports.[47–49] With the arrival of interferon-free regimens, it is still unknown whether they are associated with a change in the rate of ITP during therapy and after a sustained virologic response.

Nondiabetic Endocrine Manifestations of Hepatitis C Virus Infection

HCV infection may lead to various endocrine extrahepatic manifestations in addition to diabetes mellitus type 2 (**Table 3**). In the following sections, we aim to give an overview of current literature on frequent as well as rare endocrine diseases with a potential association with HCV. Notwithstanding, the great majority of evidence is based on small, case-control studies that may be subject to selection biases and selective reporting. In many cases, information on the degree of resulting cirrhosis is lacking; therefore, the effect of HCV infection in noncirrhotic patients may not be accurately measurable.

Thyroid disease

Autoimmune thyroiditis Autoimmune thyroiditis has largely been recognized as a common extrahepatic endocrine manifestation of HCV with the first case reports in the early 1990s.[50] Additionally, Tran and colleagues[51] detected a significant association between HCV seropositivity and Hashimoto's thyroiditis when compared with hepatitis B surface antigen–positive controls, which may indicate an HCV-specific effect on the thyroid gland. Thyroid antibodies are very frequent in HCV infection and reach a prevalence of up to 42% in this population.[52] Conversely, HCV antibodies were significantly increased in 112 patients with autoimmune thyroiditis, as compared with 88 controls with nontoxic goiter (11.6% vs 2.3%; $P<.05$).[53] Another cross-sectional study among randomly selected patients with Hashimoto's thyroiditis found a highly significantly increased prevalence of HCV seropositivity compared with patients with either nontoxic goiter, myxedema, or Grave's disease.[54] In a case-control study, patients with untreated HCV infection without hepatocellular carcinoma or cirrhosis (n = 630) were more likely to present with hypothyroidism and positive antithyroglobulin, and antithyroid peroxidase antibodies than healthy controls from both iodine-sufficient (n = 268) and -deficient areas (n = 389) and HBV-infected patients.[55] In the past, several indirect mechanisms were discussed as potential links

Table 3
Nondiabetic endocrine manifestations of HCV infection

Authors	Design	Study Population	Results/Conclusion
Autoimmune thyroiditis			
Tran et al,[51] 1993	Cross-sectional study	72 chronic HCV patients before IFN therapy vs 60 chronic HBsAg-positive patients	Significant association between chronic HCV infection and prevalent thyroid autoantibodies ($P = .02$), whereas only one HbsAg-positive man had thyroid microsome autoantibodies.
Testa et al,[53] 2006	Case-control study	112 patients with autoimmune thyroid disease vs 88 patients with nontoxic goiter	Significant association between positive HCV antibodies and autoimmune thyroid disease, compared with HbsAg/anti-Hbs positive controls (11.6% vs 2.3%; $P<.05$).
Duclos-Vallée et al,[54] 1994	Cross-sectional study	200 patients with thyroid disease (50 with simple goiter, 50 with Graves' disease, 50 with Hashimoto's thyroiditis, 50 with myxedema)	12 of 50 patients with Hashimoto's thyroiditis had a positive ELISA for HCV RNA, whereas only 3 of 100 patients with other thyroid diseases were seropositive ($P<.01$). Comparable results from recombinant immunoblot assay ($P = .01$).
Nair Kesavachandran et al,[61] 2013	Systematic review	HCV patients receiving IFN treatment (both single and combination treatment)	Other risk factors than IFN treatment may account for the association between HCV infection and thyroid-related disorders. Validity of pooled risk estimates limited (high variability, variation in IFN criteria, dosage, and treatment.
Thyroid cancer			
Fiorino et al,[67] 2015	Systematic review	Studies on the association between HCV infection and different cancer types	No definitive and univocal conclusion for the association between HCV and thyroid cancer.
Amin et al,[65] 2006	Retrospective data-linkage study	75,834 HCV vs 39,109 HBV vs 2604 HBV/HCV coinfected patients	Lower incidence rate of thyroid cancer in HCV monoinfected patients, as compared with incidence from the New South Wales Central Cancer Registry (SIR = 0.3; 95% CI, 0.2–0.7; $P<.05$).
Giordano et al,[66] 2007	Retrospective data-linkage study	146,394 HCV-infected patients vs 572,293 seronegative patients	No association between HCV infection and thyroid cancer (adjusted HR, 0.72; 95% CI, 0.52–0.99; $P = .04$).

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Table 3
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Authors	Design	Study Population	Results/Conclusion
Montella et al,[63] 2001	Case-control study	495 patients with different cancer types (130 with thyroid cancer) vs 226 healthy controls	Significant association between HCV and thyroid cancer (OR, 2.8; 95% CI, 1.2–6.3; $P = .01$).
Antonelli et al,[62] 1999	Case-control study	139 patients with HCV infection vs 835 individuals from a population-based study in an iodine-deficient area in Italy	Significantly higher prevalence of papillary thyroid cancer among patients with HCV infection compared with controls (no exact figures, Fisher's exact test $P<.01$).
Male infertility			
Yang et al,[76] 2015	Case-control study	Couples undergoing in-vitro fertilization: 90 HCV-infected women only vs 78 HCV-infected men only vs 1256 noninfected controls	Similar sperm parameters, ovarian stimulation, fertilization, and pregnancy results across subgroups. HCV infection may have no effect on IVF treatment outcomes.
El-Serafi et al,[70] 2016	Case-control study	55 male patients with HCV infection vs 21 healthy controls	Increased androstenedione, prolactin, and testosterone, but decreased dehydroepiandrosterone sulfate levels in HCV-infected men vs controls (all $P<.01$).
Durazzo et al,[71] 2006	Case-control study	10 HCV-infected men before and during treatment with IFN and ribavirin at 6 and 12 months vs 16 healthy controls	Lower nemaspermic motility and morphology, lower testosterone and inhibin B levels in HCV-infected men vs controls (all $P<.01$). Treatment improved spermatic function and increased testosterone and inhibin B levels.
Menopause			
Calvet et al,[73] 2015	Prospective cohort study	667 HIV-infected women	HCV coinfection was an additional risk factor for menopause earlier than 45 y of age compared with HIV-monoinfected women (HR, 6.26; 95% CI, 2.12–18.52; $P<.01$).
Cieloszyk et al,[72] 2009	Cross-sectional study	559 middle-aged, impoverished women	Women infected with HCV were more likely to be postmenopausal than were uninfected women (age-adjusted OR, 1.68; 95% CI, 1.02–2.77; $P = .04$).

IVF			
Yang et al,[76] 2015	Case-control study	90 couples undergoing IVF: 90 HCV-infected women only vs 78 HCV-infected men only vs 1256 noninfected controls	Similar sperm parameters, ovarian stimulation, fertilization, and pregnancy results. HCV infection may have no affection on IVF treatment outcomes.
Englert et al,[77] 2007	Case-control study	42 HCV-seropositive women vs 84 healthy controls undergoing IVF	HCV-seropositive women display a decreased ovarian response to IVF.
Pregnancy			
Pergam et al,[75] 2008	Retrospective cohort study	506 HCV-positive vs 2022 HCV-negative vs 1439 drug-using HCV-negative mothers	HCV-positive pregnant women seem to be at risk for adverse neonatal and maternal outcomes.
GH axis			
Plöckinger et al,[80] 2007	Cross-sectional study	21 HCV-infected patients before and during antiviral therapy	High rate (81%) of GH insufficiency in chronic HCV infection. Treatment leads to improvement of GH levels, while IGF-1 levels remain low.
Helaly & El-Afandy,[79] 2009	Case-control study	25 HCV-infected patients vs 15 healthy controls	IGF-1 levels were significantly lower in HCV-infected patients than in controls. Negative correlation between HCV viral load and GH levels ($P<.05$).
Adrenal insufficiency			
Ben-Shlomo et al,[78] 2014	Retrospective cohort study	4668 inpatients with random morning cortisol levels $\leq$15 μg/dL	Biochemical adrenal-cortisol insufficiency in hospitalized patients is associated with HCV infection ($P = .01$).
Bone health			
Hansen et al,[83] 2014	Comparison of 2 prospective cohort studies	12,013 HCV-infected patients vs age- and sex-matched 60,065 individuals from the general population	HCV-infected patients had increased risk of all fracture types (aIRR, 2.15; 95% CI, 2.03–2.28). In contrast, overall risk of fracture did not differ between patients with chronic vs cleared HCV infection.
Orsini et al,[84] 2013	Case-control study	60 noncirrhotic untreated men with chronic HCV infection vs 59 healthy controls (matched for age, sex, weight, AND smoking status)	Noncirrhotic untreated HCV patients have lower BMD at the femur as compared with healthy men ($P = .04$).

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Table 3
(*continued*)

Authors	Design	Study Population	Results/Conclusion
Lin et al,[85] 2012	Case-control study	69 chronic HCV-infected patients vs 275 age- and sex-matched controls	In chronic HCV infection, mean BMD, Z score, and T score at the lumbar spine were significantly lower (P<.01), whereas the rate of osteoporosis in patients aged 45–54 y was significantly higher (P = .01) than among healthy controls.
Lange et al,[86] 2011	Case-control study	468 HCV-infected, treatment-naïve patients vs 6000 healthy controls	Chronic HCV infection is associated with a higher prevalence of vitamin D deficiency compared with healthy controls (25% vs 12%, P<.01).
Arteh et al,[87] 2010	Cross-sectional study	118 consecutive patients with chronic liver disease.	In cirrhotic HCV patients, 16.3% had mild, 48.8% had moderate, and 30.2% had severe vitamin D deficiency. In HCV patients without cirrhosis, 22.8% had mild, 52.6% had moderate, and 14% had severe vitamin D deficiency. In the non–HCV-related cirrhosis group, 38.9% had mild, 27.8% had moderate, and 27.8% had severe vitamin D deficiency.
Marek et al,[82] 2015	Case-control study	80 noncirrhotic patients with HBV or HCV infection vs 40 healthy controls	In patients with chronic HBV or HCV infection, daily secretion of calcidiol was lower (P<.01), diurnal concentration of intact parathyroid hormone higher (P<.01) compared with the control group.

Abbreviations: aIRR, adjusted incidence rate ratio; anti-Hbs, antibody against hepatitis B surface protein; BMD, bone mineral density; CI, confidence interval; GH, growth hormone; GP, glycoprotein; HbsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IFN, interferon; IGF-1, insulin-like growth factor 1; IVF, in vitro fertilization; OR, odds ratio; SIR, standardized incidence ratio.

between these 2 conditions, especially the interference with self-recognition in the interaction between immune system and thyrocytes,[56,57] including molecular mimicry or cross-reactivity of HCV with thyroid antigens,[57,58] formation of heat shock proteins, and changes in major histocompatibility complex II antigens on thyrocytes.[59] Interestingly, new evidence suggests that HCV can directly infect human thyroid cell lines, potentially contributing to the persistence of viral infection and to the development of thyroid autoimmunity through additional inflammatory mechanisms.[60]

At present, interferon-based HCV treatment still plays a major role in the development in autoimmune thyroiditis, also called interferon-induced thyroiditis.[61] In the light of recent dramatic improvements in the treatment of HCV infections with a shift to interferon-free regimens based on direct-acting antiviral and host-targeted agents, their role in thyroid disease still needs to be verified.

Thyroid cancer Overall, the literature on the relationship between HCV infection and thyroid cancer is controversial. Several case-control studies identified a possible association between HCV infection and thyroid cancer. In a study by Antonelli and colleagues,[62] the prevalence of histologically confirmed papillary thyroid cancer was significantly increased in patients with HCV infection compared with healthy controls (2.2% vs 0.0%; $P<.01$). Similar evidence comes from a case-control study from South Italy with an increased risk of thyroid cancer with an OR of 2.8 for thyroid cancers among HCV-infected patients compared with seronegative peers.[63] However, these data could not be confirmed in another case-control study[64] and 2 large retrospective record-linkage studies.[65,66] In a recent systematic review from 2015, Fiorino and colleagues[67] concluded from the existing literature that previously positive results from case-control studies were not confirmed in large, prospective cohort studies, which may be owing to the different and unspecific study designs of these 2 retrospective cohort studies for thyroid cancer. Therefore, targeted prospective cohort studies on this relationship may be useful to solve this divergence.

Interaction with sexual hormones: Infertility, reproduction, menopause, and pregnancy Current data suggest that HCV infection may interact with sexual function and reproduction in male and female patients, as well as in the development of menopause in women. However, there were mostly case-control studies increasing the chance of a selection bias.

A systematic review by Garolla and colleagues[68] concluded that HCV sperm infection worsens parameters such as motility and abnormal morphology with some data suggesting an improvement in semen quality after antiviral therapy. However, sperm infection may not be the sole pathway to male infertility in this population. A case-control study including 57 patients with persistent HCV monoinfection and maintained hepatic function additionally showed significantly lower testosterone (1.43 vs 3.51 ng/mL), but higher estradiol (18.24 vs 8.6 ng/mL) and prolactin (10.0 vs 6.7 ng/mL) levels compared with healthy controls.[69] Another case-control study also indicated either a reduced sperm quality or potentially altered androgen, increased prolactin and estrogen levels.[70,71] However, a small case-control study among noncirrhotic patients with chronic hepatitis B and C found a comparable response to gonadoliberin testing in comparison with healthy controls.

Some data suggest that menopause may occur earlier in HCV-infected women than in controls[72,73] and HCV infection was found to be an additional risk factor for younger age at menopause in HIV-infected Brazilian women.[73] Overall, data for the role of HCV in conception, pregnancy, and birth are somewhat contradicting, as also described in the systematic review by Floreani.[74] Although the author concluded that there is no unfavorable effect of HCV infection in pregnancy, other studies suggest the opposite,

with low birth weight, need for assisted ventilation of the fetus, and admission to a neonatal intensive care unit.[75] Yet, future research may focus on this topic and clarify potential interactions of HCV virus with sexual hormones during this dynamic episode in women.

In reproductive medicine, a case-control study including 1424 couples undergoing in vitro fertilization with either HCV-infected men or women did not show significant alterations in sperm parameters, ovarian stimulation, fertilization, and pregnancy results.[76] In contrast, Englert and colleagues[77] showed significantly lower ovarian response to stimulation in 42 HCV-seropositive women undergoing in vitro fertilization compared with 84 healthy controls.

Overall, HCV infection may negatively impact both male and female sexual function through direct infectious mechanisms or interaction with the hormonal axis of sexual hormones. Notwithstanding, data are scarce and partly contradicting; therefore, this field still deserves future research.

Adrenal insufficiency There is evidence that HCV can infect a plethora of tissues of our body, also the adrenal gland.[3] In a cross-sectional analysis by Ben-Shlomo and colleagues,[78] patients with adrenal insufficiency showed a higher prevalence of liver disease, especially HCV infection. However, there was no information on the degree of infection. Further studies may examine the prevalence and incidence of adrenal insufficiency in larger cohort studies.

Growth hormone and insulin-like growth factor There are some data suggesting a possible affection of the growth hormone (GH) axis by HCV infection, which could also serve as a potential link to HCV-associated hyperglycemic status.[79] In a case series of 21 patients with HCV, 17 (81%) presented with severe GH insufficiency and with 9 of these having decreased insulin-like growth factor (IGF) levels. After treatment with pegylated interferon-alpha plus either ribavirin or levovirin and sustained virologic response in most of the patients, severe GH insufficiency persisted only in 4 of these. However, IGF-1 levels remained low, indicating persistent GH resistance in hepatocytes.[80] In an Egyptian case-control study of 25 chronic HCV patients, IGF-1 and GH levels were significantly lower compared with 15 controls. Moreover, there was a significantly negative correlation between HCV viral load and GH levels ($P<.05$) with a nonsignificant trend for IGF-1 levels.[79] Nevertheless, there was no clear information on the degree of cirrhosis in HCV infection, which may be a potent confounder in these associations.[81] A recent case-control study from Poland[82] investigated the GH–IGF-1 axis as well as calciotropic hormones in noncirrhotic HCV- and HBV-infected patients. Although GH concentrations were increased in these patients, IGF-1 levels were decreased in comparison with healthy controls. Considering the limitations of these studies, there may be an induction of GH resistance in the liver, which may affect IGF-1 levels and increase the chance of diabetes mellitus type 2, a condition that is discussed elsewhere.

Bone health The impact of HCV infection on bone metabolism is not well-understood.

In a cohort study including 12,013 HCV-exposed patients compared with 60,065 age- and sex-matched individuals from the general population, those with HCV had a 2-fold increased risk for all fractures and low-energy fractures.[83] Although there was no difference between cleared and chronic HCV infection, one may speculate that HCV exerts a certain influence on the endocrine regulation of bone turnover. Additionally, a small case-control study among noncirrhotic HCV-infected men showed a lower femoral bone mineral density ($P = .04$) and higher rate of osteoporosis ($P = .01$)

compared with healthy peers. However, lower levels of activity and greater immobilization were also more common in HCV-infected patients, which may be possible confounders in this association.[84] Comparable results were found for a decreased lumbar spine bone mineral density and prevalence of osteoporosis in 69 HCV-infected patients compared with 275 age- and sex-matched controls in Taiwan.[85]

Whether HCV infection directly deteriorates bone health through endocrine pathways remains controversial. A possible endocrine reason for these findings could be the comparably high prevalence of vitamin D deficiency in HCV-infected patients with and, interestingly, without cirrhosis as well.[86,87] Additionally, a Polish case-cohort study found increased levels of intact parathyroid hormone in patients with either HBV or HCV infection,[82] but this could not be confirmed in a small study among exclusively HCV-infected individuals. Overall, the role of HCV infection in the endocrine regulation of bone metabolism deserves further investigation.

SUMMARY

There is accumulating evidence of an association between HCV infection and pulmonary, endocrine extrahepatic, and hematologic manifestations. Potential mechanisms of interaction are direct infection or alteration of immune response, which may result in an increased risk for obstructive and interstitial lung disease, ITP, autoimmune thyroiditis, infertility, and potentially lung and thyroid cancers. However, findings are mostly obtained from small case-control studies. Generalizability and external validity may be highly compromised owing to different study designs and populations, residual confounding, and low statistical power. This may be the reason for divergent or inconclusive results. Future efforts are needed to study the strength of association and the linking mechanisms in this population.

REFERENCES

1. NIH Consensus Statement on Management of Hepatitis C: 2002. NIH Consens State Sci Statements 2002;19(3):1–46.
2. Blackard JT, Kemmer N, Sherman KE. Extrahepatic replication of HCV: insights into clinical manifestations and biological consequences. Hepatology 2006; 44(1):15–22.
3. Yan FM, Chen AS, Hao F, et al. Hepatitis C virus may infect extrahepatic tissues in patients with hepatitis C. World J Gastroenterol 2000;6(6):805–11.
4. Faustini A, Colais P, Fabrizi E, et al. Hepatic and extra-hepatic sequelae, and prevalence of viral hepatitis C infection estimated from routine data in at-risk groups. BMC Infect Dis 2010;10:97.
5. Kanazawa H. Relationship between hepatitis C virus infection and pulmonary disorders: potential mechanisms of interaction. Expert Rev Clin Immunol 2006;2(5): 801–10.
6. Kubo K, Yamaguchi S, Fujimoto K, et al. Bronchoalveolar lavage fluid findings in patients with chronic hepatitis C virus infection. Thorax 1996;51(3):312–4.
7. Moorman J, Saad M, Kosseifi S, et al. Hepatitis C virus and the lung: implications for therapy. Chest 2005;128(4):2882–92.
8. Goh LY, Card T, Fogarty AW, et al. The association of exposure to hepatitis B and C viruses with lung function and respiratory disease: a population based study from the NHANES III database. Respir Med 2014;108(12):1733–40.
9. Silva DR, Stifft J, Cheinquer H, et al. Prevalence of hepatitis C virus infection in patients with COPD. Epidemiol Infect 2010;138(2):167–73.

10. Kanazawa H, Hirata K, Yoshikawa J. Accelerated decline of lung function in COPD patients with chronic hepatitis C virus infection: a preliminary study based on small numbers of patients. Chest 2003;123(2):596–9.
11. Kanazawa H, Yoshikawa J. Accelerated decline in lung function and impaired reversibility with salbutamol in asthmatic patients with chronic hepatitis C virus infection: a 6-year follow-up study. Am J Med 2004;116(11):749–52.
12. Fischer WA 2nd, Drummond MB, Merlo CA, et al. Hepatitis C virus infection is not an independent risk factor for obstructive lung disease. COPD 2014;11(1):10–6.
13. Chen H-S, Xing S-R, Xu W-G, et al. Portopulmonary hypertension in cirrhotic patients: prevalence, clinical features and risk factors. Exp Ther Med 2013;5(3): 819–24.
14. Sangal RB, Taylor LE, Gillani F, et al. Risk of echocardiographic pulmonary hypertension in individuals with human immunodeficiency virus-hepatitis C virus coinfection. Ann Am Thorac Soc 2014;11(10):1553–9.
15. Demir C, Demir M. Effect of hepatitis C virus infection on the right ventricular functions, pulmonary artery pressure and pulmonary vascular resistance. Int J Clin Exp Med 2014;7(8):2314–8.
16. Renard S, Borentain P, Salaun E, et al. Severe pulmonary arterial hypertension in patients treated for hepatitis C with sofosbuvir. Chest 2016;149(3):e69–73.
17. Koenig A, Stepanova M, Saab S, et al. Long-term outcomes of lung transplant recipients with hepatitis C infection: a retrospective study of the U.S. transplant registry. Aliment Pharmacol Ther 2016;44(3):271–8.
18. Doucette KE, Halloran K, Kapasi A, et al. Outcomes of lung transplantation in recipients with hepatitis C virus infection. Am J Transplant 2016;16(8):2445–52.
19. Englum BR, Ganapathi AM, Speicher PJ, et al. Impact of donor and recipient hepatitis C status in lung transplantation. J Heart Lung Transplant 2016;35(2): 228–35.
20. Allison RD, Tong X, Moorman AC, et al. Increased incidence of cancer and cancer-related mortality among persons with chronic hepatitis C infection, 2006-2010. J Hepatol 2015;63(4):822–8.
21. Ambrosino P, Tarantino L, Criscuolo L, et al. The risk of venous thromboembolism in patients with hepatitis C. A systematic review and meta-analysis. Thromb Haemost 2016;116(4):958.
22. Aliannejad R, Ghanei M. Hepatitis C and pulmonary fibrosis: hepatitis C and pulmonary fibrosis. Hepat Mon 2011;11(2):71–3.
23. Ueda T, Ohta K, Suzuki N, et al. Idiopathic pulmonary fibrosis and high prevalence of serum antibodies to hepatitis C virus. Am Rev Respir Dis 1992;146(1): 266–8.
24. Irving WL, Day S, Johnston ID. Idiopathic pulmonary fibrosis and hepatitis C virus infection. Am Rev Respir Dis 1993;148(6 Pt 1):1683–4.
25. Arase Y, Suzuki F, Suzuki Y, et al. Hepatitis C virus enhances incidence of idiopathic pulmonary fibrosis. World J Gastroenterol 2008;14(38):5880–6.
26. Goldberg HJ, Fiedler D, Webb A, et al. Sarcoidosis after treatment with interferon-alpha: a case series and review of the literature. Respir Med 2006;100(11): 2063–8.
27. Ramos-Casals M, Mana J, Nardi N, et al. Sarcoidosis in patients with chronic hepatitis C virus infection: analysis of 68 cases. Medicine 2005;84(2):69–80.
28. Faurie P, Broussolle C, Zoulim F, et al. Sarcoidosis and hepatitis C: clinical description of 11 cases. Eur J Gastroenterol Hepatol 2010;22(8):967–72.
29. Brjalin V, Salupere R, Tefanova V, et al. Sarcoidosis and chronic hepatitis C: a case report. World J Gastroenterol 2012;18(40):5816–20.

30. Fallahi P, Ferri C, Ferrari SM, et al. Cytokines and HCV-related disorders. Clin Dev Immunol 2012;2012:468107.
31. Wu PH, Lin YT, Hsieh KP, et al. Hepatitis C virus infection is associated with an increased risk of active tuberculosis disease: a nationwide population-based study. Medicine 2015;94(33):e1328.
32. Richards DC, Mikiashvili T, Parris JJ, et al. High prevalence of hepatitis C virus but not HIV co-infection among patients with tuberculosis in Georgia. Int J Tuberc Lung Dis 2006;10(4):396–401.
33. El-Serag HB, Anand B, Richardson P, et al. Association between hepatitis C infection and other infectious diseases: a case for targeted screening? Am J Gastroenterol 2003;98(1):167–74.
34. Lomtadze N, Kupreishvili L, Salakaia A, et al. Hepatitis C virus co-infection increases the risk of anti-tuberculosis drug-induced hepatotoxicity among patients with pulmonary tuberculosis. PLoS One 2013;8(12):e83892.
35. Liu YM, Cheng YJ, Li YL, et al. Antituberculosis treatment and hepatotoxicity in patients with chronic viral hepatitis. Lung 2014;192(1):205–10.
36. Nugent D, McMillan R, Nichol JL, et al. Pathogenesis of chronic immune thrombocytopenia: increased platelet destruction and/or decreased platelet production. Br J Haematol 2009;146(6):585–96.
37. Chiao EY, Engels EA, Kramer JR, et al. Risk of immune thrombocytopenic purpura and autoimmune hemolytic anemia among 120 908 US veterans with hepatitis C virus infection. Arch Intern Med 2009;169(4):357–63.
38. DiMaggio D, Anderson A, Bussel JB. Cytomegalovirus can make immune thrombocytopenic purpura refractory. Br J Haematol 2009;146(1):104–12.
39. Cines DB, Bussel JB, Liebman HA, et al. The ITP syndrome: pathogenic and clinical diversity. Blood 2009;113(26):6511–21.
40. Pivetti S, Novarino A, Merico F, et al. High prevalence of autoimmune phenomena in hepatitis C virus antibody positive patients with lymphoproliferative and connective tissue disorders. Br J Haematol 1996;95(1):204–11.
41. Zhang W, Nardi MA, Borkowsky W, et al. Role of molecular mimicry of hepatitis C virus protein with platelet GPIIIa in hepatitis C-related immunologic thrombocytopenia. Blood 2009;113(17):4086–93.
42. Aref S, Sleem T, El Menshawy N, et al. Antiplatelet antibodies contribute to thrombocytopenia associated with chronic hepatitis C virus infection. Hematology 2009;14(5):277–81.
43. Nagamine T, Ohtuka T, Takehara K, et al. Thrombocytopenia associated with hepatitis C viral infection. J Hepatol 1996;24(2):135–40.
44. Pockros PJ, Duchini A, McMillan R, et al. Immune thrombocytopenic purpura in patients with chronic hepatitis C virus infection. Am J Gastroenterol 2002;97(8):2040–5.
45. Rajan SK, Espina BM, Liebman HA. Hepatitis C virus-related thrombocytopenia: clinical and laboratory characteristics compared with chronic immune thrombocytopenic purpura. Br J Haematol 2005;129(6):818–24.
46. Sakuraya M, Murakami H, Uchiumi H, et al. Steroid-refractory chronic idiopathic thrombocytopenic purpura associated with hepatitis C virus infection. Eur J Haematol 2002;68(1):49–53.
47. Elefsiniotis IS, Pantazis KD, Fotos NV, et al. Late onset autoimmune thrombocytopenia associated with pegylated interferon-alpha-2b plus ribavirin treatment for chronic hepatitis C. J Gastroenterol Hepatol 2006;21(3):622–3.
48. Hsiao CH, Tseng KC, Tseng CW, et al. Late-onset immune thrombocytopenic purpura after withdrawal of interferon treatment for chronic hepatitis C infection: a case report. Medicine 2015;94(34):e1296.

49. Fujii H, Kitada T, Yamada T, et al. Life-threatening severe immune thrombocytopenia during alpha-interferon therapy for chronic hepatitis C. Hepatogastroenterology 2003;50(51):841–2.
50. Tran A, Quaranta JF, Beusnel C, et al. Hepatitis C virus and Hashimoto's thyroiditis. Eur J Med 1992;1(2):116–8.
51. Tran A, Quaranta JF, Benzaken S, et al. High prevalence of thyroid autoantibodies in a prospective series of patients with chronic hepatitis C before interferon therapy. Hepatology 1993;18(2):253–7.
52. Tomer Y, Villanueva R. Hepatitis C and thyroid autoimmunity: is there a link? Am J Med 2004;117(1):60–1.
53. Testa A, Castaldi P, Fant V, et al. Prevalence of HCV antibodies in autoimmune thyroid disease. Eur Rev Med Pharmacol Sci 2006;10(4):183–6.
54. Duclos-Vallée JC, Johanet C, Trinchet JC, et al. High prevalence of serum antibodies to hepatitis C virus in patients with Hashimoto's thyroiditis. BMJ 1994; 309(6958):846–7.
55. Antonelli A, Ferri C, Pampana A, et al. Thyroid disorders in chronic hepatitis C. Am J Med 2004;117(1):10–3.
56. Lunel F. Hepatitis C virus and autoimmunity: fortuitous association or reality? Gastroenterology 1994;107(5):1550–5.
57. Pastore F, Martocchia A, Stefanelli M, et al. Hepatitis C virus infection and thyroid autoimmune disorders: a model of interactions between the host and the environment. World J Hepatol 2016;8(2):83–91.
58. Martocchia A, Falaschi P. Amino acid sequence homologies between HCV polyprotein and thyroid antigens. Intern Emerg Med 2007;2(1):65–7.
59. Tomer Y, Davies TF. Infection, thyroid disease, and autoimmunity. Endocr Rev 1993;14(1):107–20.
60. Blackard JT, Kong L, Huber AK, et al. Hepatitis C virus infection of a thyroid cell line: implications for pathogenesis of hepatitis C virus and thyroiditis. Thyroid 2013;23(7):863–70.
61. Nair Kesavachandran C, Haamann F, Nienhaus A. Frequency of thyroid dysfunctions during interferon alpha treatment of single and combination therapy in hepatitis C virus-infected patients: a systematic review based analysis. PLoS One 2013;8(2):e55364.
62. Antonelli A, Ferri C, Fallahi P. Thyroid cancer in patients with hepatitis c infection. JAMA 1999;281(17):1588.
63. Montella M, Crispo A, de Bellis G, et al. HCV and cancer: a case-control study in a high-endemic area. Liver 2001;21(5):335–41.
64. Malaguarnera M, Gargante MP, Risino C, et al. Hepatitis C virus in elderly cancer patients. Eur J Intern Med 2006;17(5):325–9.
65. Amin J, Dore GJ, O'Connell DL, et al. Cancer incidence in people with hepatitis B or C infection: a large community-based linkage study. J Hepatol 2006;45(2): 197–203.
66. Giordano TP, Henderson L, Landgren O, et al. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. JAMA 2007;297(18):2010–7.
67. Fiorino S, Bacchi-Reggiani L, de Biase D, et al. Possible association between hepatitis C virus and malignancies different from hepatocellular carcinoma: a systematic review. World J Gastroenterol 2015;21(45):12896–953.
68. Garolla A, Pizzol D, Bertoldo A, et al. Sperm viral infection and male infertility: focus on HBV, HCV, HIV, HPV, HSV, HCMV, and AAV. J Reprod Immunol 2013; 100(1):20–9.

69. Hofny ER, Ali ME, Taha EA, et al. Semen and hormonal parameters in men with chronic hepatitis C infection. Fertil Steril 2011;95(8):2557–9.
70. El-Serafi AT, Osama S, El-Zalat H, et al. Dysregulation of male sex hormones in chronic hepatitis C patients. Andrologia 2016;48(1):82–6.
71. Durazzo M, Premoli A, Di Bisceglie C, et al. Alterations of seminal and hormonal parameters: an extrahepatic manifestation of HCV infection? World J Gastroenterol 2006;12(19):3073–6.
72. Cieloszyk K, Hartel D, Moskaleva G, et al. Effects of hepatitis C virus infection on menopause status and symptoms. Menopause 2009;16(2):401–6.
73. Calvet GA, Grinsztejn BG, Quintana Mde S, et al. Predictors of early menopause in HIV-infected women: a prospective cohort study. Am J Obstet Gynecol 2015;212(6):765.e1–13.
74. Floreani A. Hepatitis C and pregnancy. World J Gastroenterol 2013;19(40):6714–20.
75. Pergam SA, Wang CC, Gardella CM, et al. Pregnancy complications associated with hepatitis C: data from a 2003-2005 Washington state birth cohort. Am J Obstet Gynecol 2008;199(1):38.e1-9.
76. Yang L, Zhao R, Zheng Y, et al. Effect of hepatitis C virus infection on the outcomes of in vitro fertilization. Int J Clin Exp Med 2015;8(4):6230–5.
77. Englert Y, Moens E, Vannin AS, et al. Impaired ovarian stimulation during in vitro fertilization in women who are seropositive for hepatitis C virus and seronegative for human immunodeficiency virus. Fertil Steril 2007;88(3):607–11.
78. Ben-Shlomo A, Mirocha J, Gwin SM, et al. Clinical factors associated with biochemical adrenal-cortisol insufficiency in hospitalized patients. Am J Med 2014;127(8):754–62.
79. Helaly GF, El-Afandy NM. Influence of HCV infection on insulin-like growth factor 1 and proinflammatory cytokines: association with risk for growth hormone resistance development. Egypt J Immunol 2009;16(2):115–24.
80. Plöckinger U, Kruger D, Bergk A, et al. Hepatitis-C patients have reduced growth hormone (GH) secretion which improves during long-term therapy with pegylated interferon-alpha. Am J Gastroenterol 2007;102(12):2724–31.
81. Caufriez A, Reding P, Urbain D, et al. Insulin-like growth factor I: a good indicator of functional hepatocellular capacity in alcoholic liver cirrhosis. J Endocrinol Invest 1991;14(4):317–21.
82. Marek B, Kajdaniuk D, Niedziolka D, et al. Growth hormone/insulin-like growth factor-1 axis, calciotropic hormones and bone mineral density in young patients with chronic viral hepatitis. Endokrynol Pol 2015;66(1):22–9.
83. Hansen AB, Omland LH, Krarup H, et al. Fracture risk in hepatitis C virus infected persons: results from the DANVIR cohort study. J Hepatol 2014;61(1):15–21.
84. Orsini LG, Pinheiro MM, Castro CH, et al. Bone mineral density measurements, bone markers and serum vitamin D concentrations in men with chronic non-cirrhotic untreated hepatitis C. PLoS One 2013;8(11):e81652.
85. Lin JC, Hsieh TY, Wu CC, et al. Association between chronic hepatitis C virus infection and bone mineral density. Calcif Tissue Int 2012;91(6):423–9.
86. Lange CM, Bojunga J, Ramos-Lopez E, et al. Vitamin D deficiency and a CYP27B1-1260 promoter polymorphism are associated with chronic hepatitis C and poor response to interferon-alfa based therapy. J Hepatol 2011;54(5):887–93.
87. Arteh J, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. Dig Dis Sci 2010;55(9):2624–8.