



# Endocrine disorders associated with hepatitis C virus chronic infection

Michele Colaci<sup>1</sup> · Lorenzo Malatino<sup>1</sup> · Alessandro Antonelli<sup>2</sup> · Poupak Fallahi<sup>2</sup> · Dilia Giuggioli<sup>3</sup> · Clodoveo Ferri<sup>3</sup>

© Springer Science+Business Media, LLC, part of Springer Nature 2018

## Abstract

The term “HCV syndrome” encompasses several organ- and systemic pathophysiological states, which often recognize autoimmunity or neoplastic evolution in their pathophysiology, as well as chronic HCV infection as trigger. The clinical features of HCV patients are heterogenous, and may include endocrine or metabolic disorders, namely autoimmune thyroiditis, type 2 diabetes mellitus, and erectile/sexual dysfunctions. In this review, we summarize current knowledge on the endocrine/metabolic diseases associated with chronic HCV infection, focusing on the main concepts emerged in the recent literature in this field. The application of this knowledge in everyday clinical practice may be relevant, in order to reinforce a holistic vision of the patient with chronic HCV infection, stimulating in turn a multi-disciplinary approach, thus increasing the probability of early diagnosis, more effective treatments, and a better prognostic outcome.

**Keywords** Hepatitis C · HCV · Diabetes · Thyroiditis · Hypothyroidism · Erectile dysfunction

## 1 Introduction

Hepatitis C (HCV)-infected patients frequently present with a variable combination of different organ and systemic autoimmune or neoplastic diseases. A number of extra-hepatic manifestations have been reported, suggesting that HCV is responsible for a systemic disorder, more severe than just a liver disease itself. The term “HCV syndrome” includes the group of hepatic and extra-hepatic disorders among which the mixed cryoglobulinemic vasculitis may be seen as the pathophysiological prototype [1, 2]. A few endocrine and metabolic diseases, such as autoimmune thyroiditis (AT), type 2 diabetes mellitus, and erectile dysfunction, may be considered part of HCV syndrome [2–7] (Table 1).

In addition to the well-known tropism for hepatocytes, HCV has tropism for other cells, particularly the B lymphocytes [8]. Therefore, HCV can stimulate complex autoimmune

alterations through benign B lymphocyte expansion into tissues chronically infected by the virus [1, 2].

In the present paper, we reviewed recent literature data regarding endocrine/metabolic disorders associated with HCV.

## 2 Thyroid diseases associated with HCV

Autoimmune thyroiditis (AT) is a prototype of organ-specific autoimmune disease: it includes two main pathophysiological and clinical entities, Hashimoto’s thyroiditis and Graves disease; nonetheless, subclinical thyroid dysfunction should be considered in the disease spectrum [9]. Clinically, AT could lead to both hypo- and hyperthyroidism, more often the first one, or it can produce modest alterations of TSH levels, without overt manifestations. Presence of AT in the course of autoimmune systemic diseases is very frequent. In particular, thyroid involvement is considered one of the most frequent endocrine disorders in association with chronic HCV infection, in the spectrum of HCV syndrome [1–10].

A large Italian population-based study published in 2004 investigated the prevalence of AT in a series of 630 HCV patients not treated with interferon-alpha (IFN). In this survey, HCV patients were more likely than the control groups to show hypothyroidism (13%), anti-thyroglobulin antibodies (TgAb) (17%), and anti-thyroperoxidase antibodies (TPOAb) (21%) [11].

A retrospective cohort study analyzing data of more than 140,000 HCV-infected male patients of US Veterans Affairs

---

✉ Michele Colaci  
michele.colaci@unict.it

<sup>1</sup> Internal Medicine Unit, Cannizzaro Hospital, Department of Clinical and Experimental Medicine, University of Catania, Via Messina, 829, 95100 Catania, Italy

<sup>2</sup> Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

<sup>3</sup> Rheumatology Unit, Azienda Ospedaliero-Universitaria di Modena, University of Modena and Reggio Emilia, Modena, Italy

**Table 1** Main endocrine/metabolic disorders associated with HCV, their pathogenetic mechanisms and outcomes

Endocrine disorders	Pathogenetic mechanism(s)	Outcome(s)
Autoimmune Thyroiditis	Up-regulation of the IFN $\gamma$ , TNF $\alpha$ inducible chemokines produced by thyrocytes infected by HCV.	Subclinical inflammation Hypothyroidism
	Th1 lymphocytes infiltration of thyroid and secretion of IFN $\gamma$ , TNF $\alpha$ , and chemokines.	Increased risk of papillary thyroid adenocarcinoma
Type 2 Diabetes Mellitus	Induction of insulin resistance in hepatocytes and peripheral cells by inhibiting glucose cell intake (GLUT-1, -2) and PI-3 K/Akt signaling pathway	Increased risk of steatosis and liver cirrhosis Increased risk of hepatocarcinoma
	Increased E2 and reduced T/E2 ratio	Impotence
Erectile/sexual dysfunction	Reduction of free T and inhibin B	Infertility
	Anti-sperm antibodies	

Legenda: PI3K, phosphatidylinositol-3-kinases; Akt, protein kinase B; GLUT, glucose transporter; E2, estrogen; T, testosterone

health-care facilities from 1997 to 2004 found that thyroiditis risk was slightly increased than in HCV negatives [12].

Moreover, in a recent meta-analysis by Shen et al. regarding the world literature on the topic, prevalence of TgAb, TPOAb, and anti-thyroid microsomal antibody were respectively 2.40-, 1.96- and 1.86-fold higher in HCV-positive subjects than in controls. Moreover, the hypothyroidism risk was 3.10 (95% CI 2.19–4.40) in HCV-infected patients [5].

An established association between chronic HCV infection and AT was first identified by an Italian case–control prospective study, including 93 patients affected by HCV-related mixed cryoglobulinemia, including 93 patients with isolated HCV hepatitis, and 93 age/gender-matched healthy subjects living all in the same geographical area as controls [12]. AT, subclinical hypothyroidism, and the presence of isolated specific serum autoantibodies, i.e., TPOAb and/or TgAb, were more frequent in the first group than controls (35% vs. 16%, 11% vs. 2%, 31% vs. 12%, respectively). Moreover, higher frequency of AT was recorded among cryoglobulinemic patients in comparison with hepatopathic patients (35% vs. 22%), with a significant high prevalence of TPOAb (28% vs. 14%). Finally, hypothyroidism was associated with higher cryocrit and with the presence of other autoantibody positivity, as well as with longer mixed cryoglobulinemic vasculitis duration, presence of proteinuria, or active hepatitis [13, 14].

Noteworthy, even the prevalence of papillary thyroid cancer resulted higher in HCV patients, especially in presence of cryoglobulinemic vasculitis [15]. This finding supported the hypothesis of the oncogenic potential of HCV through the direct infection of thyrocytes and the probable contribution of the same pathogenetic process responsible for AT [16]. Indeed, the same oncogenic multistep process already demonstrated for HCV lymphotropism, from “benign” B cell proliferation to lymphomagenesis [8, 17], may be supposed in the facilitation of neoplastic evolution in thyroid gland.

An important contribution to understand the mechanisms involved in the pathogenesis of thyroid disorders among HCV

patients was given by Blackard et al., who demonstrated that the virus may infect a human thyroid cell line (ML1), which shows the membrane expression of an important HCV receptor, that is CD81 [18]. Furthermore, HCV does extensively alter the immune system homeostasis, so inducing a prevalent T helper-1 response in the target tissues that ultimately produces chronic inflammation and fibrosis [19, 20]. Several studies by Antonelli A et al. reported the up-regulation of the IFN-gamma, TNF-alpha inducible CXCL9, CXCL10, CXCL11 chemokines, as well as IL-6, in the serum of AT patients with and without mixed cryoglobulinemia [21–25]. Briefly, the direct infection of thyrocytes by HCV up-regulates gene expression of C-X-C motif IFN-gamma inducible chemokines, which are secreted in a paracrine manner by thyrocytes themselves. As a consequence, Th1 lymphocytes are recruited, leading to the formation of inflammatory infiltrates harbored in the thyroid parenchyma. In turn, T cells secrete TNF-alpha and IFN-gamma, which stimulate chemokines production by thyrocytes as a vicious cycle, so perpetuating organ inflammation and tissue damage [4, 26]. Overall, HCV may lead toward chronic stimulation of the immune system, namely the T-helper 1 lymphocytes that in turn perpetuate the immune cascade and increasing the levels of the chemokines cited above [4, 26].

The sustained activation of the immune system at the basis of thyroid immune-mediated damage by HCV could eventually led to thyroid cancer [16, 27]. A high prevalence of papillary thyroid cancer was first observed in a cohort of 139 HCV patients (2.2%), and no cancer cases in the 835 controls [28]; subsequently, Montella M et al. confirmed this result, finding a significant association between HCV and thyroid cancer (OR = 2.8, 95%CI 1.2–6.3) [29]. AT, especially in presence of higher TSH levels, was recognized to be a predisposing condition for thyroid cancer, in a multistep process that includes mutated oncogenes mutation and persistent stimulation of thyrocytes by TSH [30].

AT diagnosis is relatively simple and is based on the presence of the main autoantibodies of AT (TPOAb and TgAb)

and the heterogeneous, hypoechogenic texture of the gland, up to the pseudo-nodular pattern. On the basis of the relative feasibility of AT diagnosis using reliable, not invasive or expensive exams, all HCV patients, mainly in the case of coexistence of mixed cryoglobulinemia, should undergo thyroid evaluation periodically [31].

In the majority of HCV patients, AT is a silent feature of the clinical picture [3–5]; otherwise, hypothyroidism, generally subclinical, may develop, so requiring the standard hormone replacement therapy.

### 3 Type 2 diabetes mellitus and HCV

As early as 2008 a systematic review, combining data from 34 studies and covering more than 300,000 patients, found a pooled adjusted odds ratio for type 2 diabetes in HCV patients of approximately 1.7 [32], therefore emphasizing that HCV patients harbour a 70% increase of the relative risk to develop type 2 diabetes. A recent meta-analysis demonstrated a clear-cut association between HCV infection and type 2 diabetes: namely, HCV infection is associated with an increased risk of diabetes, independently from the severity of the associated liver disease [33]. HCV seropositivity was found to be an important risk factor (about 3-fold increased risk) even for new-onset diabetes after kidney transplantation, according to a population-based retrospective study on 557 Chinese subjects [34]. Interestingly, a Korean population-based cohort study including more than 500,000 persons found that the hazard ratio of diabetes was the highest in the co-infected HCV/HBV group, (HR 1.90) and increased in HCV and HBV groups (HR 1.68, 1.41, respectively), in comparison with non-infected subjects [35]. On the contrary, in a cohort of 7149 patients with chronic HCV hepatitis from Hong Kong, patients co-infected by HBV showed similar prevalence of diabetes compared with the mono-infection subgroup [36]. Consistently, in the meta-analysis by Fabiani S et al. HBV infection prevalences in diabetic and non-diabetic subjects were not significantly different [33].

The association between HCV and diabetes was also demonstrated by studies evaluating cohorts of diabetics. Farshadpour F et al. reported that patients affected by type 2 diabetes presented a almost 4-fold higher frequency of HCV infection than non diabetic subjects in an Iranian cohort, with a seroprevalence of HCV in 11 out 556 (1.98%) patients [37]. In a multicentre Italian cohort of diabetics, the prevalence of HCV-infected patients was higher (51/859, 5.9%), in comparison with 1.6% of HBV-infected subjects; the Authors underlined the importance of serological screening for diabetics, since viral seropositivity may long remain undiagnosed [38].

The link between chronic HCV infection and type 2 diabetes is not a trivial or an epidemiological association. Both these pathological conditions influence each other as well as their clinical manifestations and prognosis.

Several Authors found that diabetes mellitus is a significant risk factor for the development of liver cirrhosis in HCV patients [39, 40]. In a case-control study by Li X et al. carried out in 210 Chinese HCV-related hepatopatic patients, diabetes increased by two times the risk to develop cirrhosis (adjusted odds ratio 2.13; 95% CI, 1.34–3.38) [39]. In addition, development of hepatic steatosis is facilitated and fibrosis progresses more rapidly in presence of diabetes [41, 42]. In fact, high glucose and hyperinsulinemia stimulate the secretion of matrix proteins and other precursors of hepatic fibrosis by hepatic stellate cells, through over-expression of connective tissue growth factor [43].

Current research has already elucidated some underlying mechanisms that make HCV patients more prone to develop type 2 diabetes. The abnormalities of carbohydrate metabolism, such as hyperinsulinemia and insuline resistance, often part of metabolic syndrome, are known to be associated with chronic hepatic diseases, but they cannot justify per se the association between diabetes and HCV. HCV-driven chronic inflammatory processes may contribute to the development of diabetes. Nonetheless, viral proteins can interfere on the regulation of metabolism and insulin signalling.

In this respect, Kasai D et al. demonstrated that the surface expression of Glucose Transporters (GLUT-1 and 2) was suppressed in cells infected by HCV as compared with controls, and that IFN- $\alpha$  restored glucose uptake, GLUT-2 surface expression, mRNA expression and GLUT-2 promoter activities. [44]. The impairment of glucose uptake and the consequent promotion of insulin resistance may be due also to the increased TNF- $\alpha$  production together with an enhancement of the suppressor of cytokine (SOC-3); both events inhibiting PI3K and Akt phosphorylation, which led to the surface expression of the GLUT-4 [45]. Moreover, HCV core protein itself increases Ser<sup>312</sup> phosphorylation of IRS-1, which in turn decreases Tyr phosphorylation of IRS-1. These pathways might interfere with the association of IRS-1 with the insulin receptor, impair the PI-3 K/Akt signaling pathway, and negatively regulate IRS-1 function. The final result is the decrease of insulin-induced glucose uptake by hepatocytes. [46].

The insulin resistance in HCV subjects may be caused also by the propagation of inflammatory factors such as TNF- $\alpha$  or monocyte chemoattractant protein-1, released from HCV-induced liver inflammation [47, 48]. Furthermore, HCV itself may also directly activate the mTOR/S6K1 signaling pathway, inhibiting IRS-1 protein function, thus down-regulating GLUT-4, and up-regulating the gluconeogenic enzyme phosphoenolpyruvate carboxykinase-2 [49].

In a recent study by Singhal A et al., HCV infection-derived miRNAs (namely miR-122) has been proposed as a pivotal player in the development of diabetes [50]. In this respect, it is well recognized that circulating miRNAs could modulate gene expression in peripheral tissues, leading in turn to the development of insulin resistance and diabetes.

Of note, in HCV patients, the coexistence of diabetes is associated with a worse liver-related prognosis, because of increased frequencies of liver cirrhosis and occurrence of hepatocarcinoma. [51, 52]. As a consequence, treatment of diabetes by metformin and thiazolidinediones seems to lower the risk of hepatocarcinoma, liver-related death or liver transplantation [53, 54].

On the other hand, improvement of insulin resistance may be included among the effects of sustained virological response [55, 56], even considering the use of IFN-free therapies with the new direct-acting antivirals [57, 58]. Indeed, the achievement of sustained viral response had led to lower incidence of diabetes during the IFN era of HCV therapy. Nowadays, the direct-acting antiviral drugs, which are the gold standard for treating HCV infection, are associated with better fasting glucose and glycated hemoglobin levels [57–60]. Furthermore, a role for the new antivirals was also reported to reduce serum level of total cholesterol and triglycerides, along with values of blood pressure, thus lowering the global cardiovascular risk in HCV treated patients [59]. In general, sustained virological response achievement in HCV patients correlates with reduced extra-hepatic mortality (OR 0.44, 95%CI 0.28–0.67), complete remission in cryoglobulinemic patients (OR 20.76, 95%CI 6.73–64.05), and impaired incidence of diabetes (OR 0.34, 95%CI 0.21–0.56) [61].

Overall, HCV favors insulin resistance impairing hepatic and peripheral glucose uptake. As a consequence, it should be considered a risk factor for type 2 diabetes development [61]. In parallel, coexistence of diabetes is a negative prognostic factor for HCV patients because of the stimulation of liver fibrosis/steatosis. Therefore glucose-lowering drugs may improve the prognosis of cirrhotics [62].

Clinically, HCV patients with diabetes are not different from the other diabetics. As early as 2002, Akbar DH et al., evaluating a cohort of 35 anti-HCV positive Saudi diabetics, reported a higher body-mass index than non-diabetics and a frequent family history of diabetes [63]. The increased prevalence of liver steatosis and fibrosis (already discussed above) in comparison with HCV patients without diabetes is well known in the literature [64]. However, an attenuated diabetic phenotype has been described for HCV-related cryoglobulinemic diabetics, namely lower BMI, lower blood pressure values, lower total and LDL cholesterol concentrations, as compared with non-HCV diabetics [65].

## 4 Sexual dysfunction in HCV patients

Erectile dysfunction is a frequent condition that impairs the quality of life of HCV patients [7]. However, this disorder is often underestimated by physicians, who are

focused on other more life-threatening clinical features, or due to the fact that patients feel uncomfortable when they talk about such a dysfunction.

In Countries where HCV prevalence is high (i.e. Egypt), chronic HCV infection should be considered in the differential diagnosis of erectile dysfunction, bearing in mind that the frequency of andrologic disorders in HCV subjects ranges nearly 30%, mainly in patients with liver cirrhosis [66].

A strong association between severity of erectile dysfunction and chronic HCV was demonstrated, along with statistically significant increase of estrogen and reduction in IGF-1 levels. [67]. Interestingly, Wang FP et al., evaluating a cohort of 131 Chinese HCV patients versus healthy controls, showed that levels of estrogen (E2) and testosterone (T) as well as the T/E2 ratio among women were similar between patients and healthy controls; on the contrary, among men, levels of E2 were higher and the T/E2 ratio was lower in HCV patients than in controls [68]. Of note, a cross-sectional study in 308 male veterans with chronic HCV infection demonstrated that higher total serum T levels were associated with an increased risk of hepatic fibrosis and inflammatory activity, independently of other known or biologically-plausible strong potential confounders [69]. Furthermore, 17beta-estradiol can inhibit HCV life cycle, mainly interfering with the late phases of assembly and release of virus from cells [70].

In female Egyptian patients, HCV (genotype 4) infection is associated with increased hormonal levels of E2, total T, and progesterone. However, while estradiol and progesterone levels decreased with age, T raises [71]. This study suggests that women of reproductive age had lower disease severity compared to menopausal women, hypothesizing a pathogenic role for the observed changes in the sex hormonal levels. In fact, menopausal women exhibited greater disease severity, probably due to the decline in E2 and progesterone and the rise in total T level occurring with menopause [71]. These findings should be confirmed with additional studies to further assess the possible influence of sexual hormones in the prognosis of patients with chronic HCV hepatitis.

Sexual impotence should be framed among several other indirect consequences of chronic HCV infection, which together produce a decisive impact on patients' psychology [72]. Namely, decreased muscle mass, redistribution of body fat, gynecomastia in men, etc. largely modify patients' self image, leading to decreased sexual desire, loss of self-esteem, up to depression [72, 73].

Finally, a possible negative influence of virus on spermatogenesis was proposed in a preliminary controlled study, in terms of nemaspermic motility and morphology, along with lower levels of free T and inhibin B, a hormone secreted by Sertoli cells that is considered a sensible marker of active spermatogenesis [74]. Subsequently, Hofny ET et al. confirmed the negative effect of HCV on



spermatogenesis, with significant decrease in semen volume, sperm count and motility, and increased percentage of abnormal sperm morphology, as compared with controls [75]. Moreover, sperm alterations were negatively correlated with the duration of the HCV infection and the viral load [75]. The mechanism responsible for HCV-related spermatogenesis impairment could involve the development of anti-sperm antibodies, underlining the trigger role of the virus in generating autoimmune processes [76].

## 5 Conclusions

Chronic HCV infection is responsible of a multi-organ, systemic pathological condition whose pathophysiology may include chronic inflammatory-based damage, autoimmune processes, and neoplastic evolution. As a consequence, HCV patients' clinical picture is not restricted to chronic hepatitis, which presents different severity grades from subclinical inflammation to overt liver cirrhosis. Indeed, several nosographic entities may be associated with chronic HCV infection, ranging from single organ disorders to complex multi-system disorders. The term "HCV syndrome" was proposed in order to unify all these pathological entities that recognize HCV as the main trigger [1, 2]. As part of HCV syndrome, a few endocrine/metabolic diseases are nosographically considered, namely AT, type 2 diabetes mellitus, and sexual dysfunction. A subset of each of these diseases may be recognized as HCV-related [1–9].

The fallout of these concepts in everyday clinical practice may be relevant, since it emphasizes the hypothesis of an aetiologic therapy for chronic diseases considered not susceptible of definitive healing, up to date. In particular, the recent introduction of several new antivirals into the physician's armamentarium has made the hypothesis of a definite treatment more accessible. However, the actual effects of sustained virological response on long-term prognosis of HCV-associated autoimmune or neoplastic diseases are not definitely clarified, thus further studies are necessary.

Another important consequence of the identification of HCV syndrome should be the recovery of a holistic vision of the patients with chronic HCV infection, thanks to a multi-disciplinary approach to these patients, leading to a higher probability of early diagnosis, then more effective treatments and a better outcome.

Overall, HCV syndrome remains a useful educational prototype of virus-driven autoimmune and neoproliferative multi-system disorder [1, 2, 77]. The study of HCV syndrome represents one of the most successful research area of translational medicine, in term of aetiopathophysiology understanding and clinical application.

## Compliance with ethical standards

**Conflict of interests** Michele Colaci, Lorenzo Malatino, Alessandro Antonelli, Poupak Fallahi, Dilia Giuggioli, and Clodoveo Ferri declare no conflict of interests.

## References

1. Ferri C, Antonelli A, Mascia MT, Sebastiani M, Fallahi P, Ferrari D, et al. HCV-related autoimmune and neoplastic disorders: the HCV syndrome. *Dig Liver Dis*. 2007;39(Suppl 1):S13–21.
2. Ferri C, Sebastiani M, Giuggioli D, Colaci M, Fallahi P, Piluso A, et al. Hepatitis C virus syndrome: a constellation of organ- and non-organ specific autoimmune disorders, B-cell non-Hodgkin's lymphoma, and cancer. *World J Hepatol*. 2015 Mar 27;7(3):327–43.
3. Ferrari SM, Fallahi P, Mancusi C, Colaci M, Manfredi A, Ferri C, et al. HCV-related autoimmune disorders in HCV chronic infection. *Clin Ter*. 2013;164(4):e305–12.
4. Antonelli A, Ferri C, Ferrari SM, Colaci M, Sansonno D, Fallahi P. Endocrine manifestations of hepatitis C virus infection. *Nat Clin Pract Endocrinol Metab*. 2009;5:26–34.
5. Shen Y, Wang XL, Xie JP, Shao JG, Lu YH, Zhang S, et al. Thyroid disturbance in patients with chronic hepatitis C infection: a systematic review and meta-analysis. *J Gastrointest Liver Dis*. 2016;25: 227–34.
6. Desbois AC, Cacoub P. Diabetes mellitus, insulin resistance and hepatitis C virus infection: a contemporary review. *World J Gastroenterol*. 2017 Mar 7;23(9):1697–711.
7. Gentile I, Fusco F, Buonomo AR, Scotto R, Zappulo E, Pinchera B, et al. Prevalence and risk factors of erectile dysfunction in patients with hepatitis B virus or hepatitis C virus or chronic liver disease: results from a prospective study. *Sex Health* 2018;in press.
8. Ferri C, Monti M, La Civita L, Longombardo G, Greco F, Pasero G, et al. Infection of peripheral blood mononuclear cells by hepatitis C virus in mixed cryoglobulinemia. *Blood*. 1993 Dec 15;82(12): 3701–4.
9. Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. Autoimmune thyroid disorders. *Autoimmun Rev*. 2015;14:174–80.
10. Di Domenicantonio A, Politti U, Marchi S, De Bortoli N, Giuggioli D, Antonelli A, et al. A review on thyroid autoimmune disorders and HCV chronic infection. *Clin Ter*. 2014;165:e376–81.
11. Antonelli A, Ferri C, Pampana A, Fallahi P, Nesti C, Pasquini M, et al. Thyroid disorders in chronic hepatitis C. *Am J Med*. 2004;117:10–3.
12. Giordano TP, Henderson L, Landgren O, Chiao EY, Kramer JR, El-Serag H, et al. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. *JAMA*. 2007;297:2010–7.
13. Antonelli A, Ferri C, Fallahi P, Giuggioli D, Nesti C, Longombardo G, et al. Thyroid involvement in patients with overt HCV-related mixed cryoglobulinemia. *QJM*. 2004;97:499–506.
14. Ferri C, Colaci M, Fallahi P, Ferrari SM, Antonelli A, Giuggioli D. Thyroid involvement in hepatitis C virus-infected patients with/without mixed cryoglobulinemia. *Front Endocrinol*. 2017;8:159.
15. Wang P, Jing Z, Liu C, Xu M, Wang P, Wang X, et al. Hepatitis C virus infection and risk of thyroid cancer: a systematic review and meta-analysis. *Arab J Gastroenterol*. 2017;18:1–5.
16. Akeno N, Blackard JT, Tomer Y. HCV E2 protein binds directly to thyroid cells and induces IL-8 production: a new mechanism for HCV induced thyroid autoimmunity. *J Autoimmun*. 2008;31:339–44.

17. Zignego AL, Gragnani L, Piluso A, Sebastiani M, Giuggioli D, Fallahi P, et al. Virus-driven autoimmunity and lymphoproliferation: the example of HCV infection. *Expert Rev Clin Immunol*. 2015;11: 15–31.
18. Blackard JT, Kong L, Huber AK, Tomer Y. Hepatitis C virus infection of a thyroid cell line: implications for pathogenesis of HCV and thyroiditis. *Thyroid*. 2012;23:863–70.
19. Fallahi P, Ferrari SM, Giuggioli D, Sebastiani M, Colaci M, Ferri C, et al. Chemokines in the pathogenesis and as Therapeutical markers and targets of HCV chronic infection and HCV extrahepatic manifestations. *Curr Drug Targets*. 2017;18(7):786–93.
20. Fallahi P, Ferri C, Ferrari SM, Corrado A, Sansonno D, Antonelli A. Cytokines and HCV-related disorders. *Clin Dev Immunol*. 2012;2012:468107.
21. Antonelli A, Ferri C, Ferrari SM, De Marco S, Di Domenicantonio A, Centanni M, et al. Interleukin-1 $\beta$ , C-x-C motif ligand 10, and interferon-gamma serum levels in mixed cryoglobulinemia with or without autoimmune thyroiditis. *J Interf Cytokine Res*. 2010;30: 835–42.
22. Antonelli A, Fallahi P, Ferrari SM, Colaci M, Giuggioli D, Saraceno G, et al. Increased CXCL9 serum levels in hepatitis C-related mixed cryoglobulinemia, with autoimmune thyroiditis, associated with high levels of CXCL10. *J Interf Cytokine Res*. 2013;33:739–45.
23. Antonelli A, Fallahi P, Ferrari SM, Sebastiani M, Manfredi A, Mazzi V, et al. Circulating CXCL11 and CXCL10 are increased in hepatitis C-associated cryoglobulinemia in the presence of autoimmune thyroiditis. *Mod Rheumatol*. 2012;22:659–67.
24. Antonelli A, Ferri C, Ferrari SM, Di Domenicantonio A, Ferrari P, Pupilli C, et al. The presence of autoimmune thyroiditis in mixed cryoglobulinemia patients is associated with high levels of circulating interleukin-6, but not of tumor necrosis factor- $\alpha$ . *Clin Exp Rheumatol*. 2011;29(1 Suppl 64):S17–22.
25. Antonelli A, Ferrari SM, Frascerra S, Galetta F, Franzoni F, Corrado A, et al. Circulating chemokine (CXC motif) ligand (CXCL)9 is increased in aggressive chronic autoimmune thyroiditis, in association with CXCL10. *Cytokine*. 2011 Aug;55(2):288–93.
26. Fallahi P, Ferrari SM, Politti U, Giuggioli D, Ferri C, Antonelli A. Autoimmune and neoplastic thyroid diseases associated with hepatitis C chronic infection. *Int J Endocrinol*. 2014;2014:935131.
27. Antonelli A, Ferri C, Ferrari SM, Colaci M, Fallahi P. Immunopathogenesis of HCV-related endocrine manifestations in chronic hepatitis and mixed cryoglobulinemia. *Autoimmun Rev*. 2008;8:18–23.
28. Antonelli A, Ferri C, Fallahi P. Thyroid cancer in patients with hepatitis C infection. *JAMA*. 1999 May 5;281(17):1588.
29. Montella M, Crispo A, de Bellis G, Izzo F, Frigeri F, Ronga D, et al. HCV and cancer: a case-control study in a high-endemic area. *Liver*. 2001 Oct;21(5):335–41.
30. Fiore E, Rago T, Latrofa F, Provenza MA, Piaggi P, Delitala A, et al. Hashimoto's thyroiditis is associated with papillary thyroid carcinoma: role of TSH and treatment with L-thyroxine. *Endocr Relat Cancer*. 2011;18:429–37.
31. Ferri C, Ramos-Casals M, Zignego AL, Arcaini L, Roccatello D, Antonelli A, et al. ISG-EHCV coauthors. International diagnostic guidelines for patients with HCV-related extrahepatic manifestations. A multidisciplinary expert statement. *Autoimmun Rev*. 2016 Dec;15(12):1145–60.
32. White DL, Ratzliff V, El-Serag HB. Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. *J Hepatol*. 2008;49(5):831–44.
33. Fabiani S, Fallahi P, Ferrari SM, Miccoli M, Antonelli A. Hepatitis C virus infection and development of type 2 diabetes mellitus: Systematic review and meta-analysis of the literature. *Rev Endocr Metab Disord*. 2018;in press.
34. Liang J, Lv C, Chen M, Xu M, Zhao C, Yang Y, Wang J, Zhu D, Gao J, Rong R, Zhu T, Yu M. Effects of preoperative hepatitis B virus infection, hepatitis C virus infection, and co-infection on the development of new-onset diabetes after kidney transplantation. *J Diabetes*. 2018;in press.
35. Choi HY, Kim Y, Cho H, Kim BH, Ki M. Risk of diabetes in viral hepatitis B or C patients compared to that in noninfected individuals in Korea, 2002–2013: a population-based cohort study. *J Viral Hepat*. 2018 Mar;25(3):272–80.
36. Subramaniam S, Wong VW, Tse YK, Yip TC, Chan HL, Wong GL. Impact of diabetes mellitus and hepatitis B virus coinfection on patients with chronic hepatitis C: a territory-wide cohort study. *J Gastroenterol Hepatol*. 2018 Apr;33(4):934–41.
37. Farshadpour F, Taherkhani R, Ravanbod MR, Eghbali SS. Prevalence and genotype distribution of hepatitis C virus infection among patients with type 2 diabetes mellitus. *Med Princ Pract*. 2018;27(4):308–16.
38. Soverini V, Persico M, Bugianesi E, Forlani G, Salamone F, Masarone M, et al. HBV and HCV infection in type 2 diabetes mellitus: a survey in three diabetes units in different Italian areas. *Acta Diabetol*. 2011;48:337–43.
39. Li X, Gao Y, Xu H, Hou J, Gao P. Diabetes mellitus is a significant risk factor for the development of liver cirrhosis in chronic hepatitis C patients, particularly for women. *Sci Rep*. 2017 Aug 22;7(1):9087.
40. Cao LH, Lu FM, Lu XJ, Zhu LY. Study on the relationship between insulin growth factor 1 and liver fibrosis in patients with chronic hepatitis C with type 2 diabetes mellitus. *J Cell Biochem*. 2018;in press.
41. Bakulin IG, Sandler YG, Vinnitskaya EV, Keiyan VA, Rodionova SV, Rotin DL. Diabetes mellitus and nonalcoholic fatty liver disease: the verges of contingency. *Ter Arkh*. 2017;89:59–65.
42. Hui JM, Sud A, Farrell GC, Bandara P, Byth K, Kench JG, et al. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression. *Gastroenterology*. 2003;125: 1695–704.
43. Paradis V, Perlemuter G, Bonvoust F, Dargere D, Parfait B, Vidaud M, et al. High glucose and hyperinsulinemia stimulate connective tissue growth factor expression: a potential mechanism involved in progression to fibrosis in nonalcoholic steatohepatitis. *Hepatology (Baltimore, Md.)*. 2001;34:738–44.
44. Kasai D, Adachi T, Deng L, Nagano-Fujii M, Sada K, Ikeda M, et al. HCV replication suppresses cellular glucose uptake through down-regulation of cell surface expression of glucose transporters. *J Hepatol*. 2009;50:883–94.
45. Romero-Gómez M. Insulin resistance and hepatitis C. *World J Gastroenterol*. 2006;12:7075–80.
46. Banerjee S, Saito K, Ait-Goughoulte M, Meyer K, Ray RB, Ray R. Hepatitis C virus core protein upregulates serine phosphorylation of insulin receptor substrate-1 and impairs the downstream akt/protein kinase B signaling pathway for insulin resistance. *J Virol*. 2008;82: 2606–12.
47. Knobler H, Zhornitsky T, Sandler A, Haran N, Ashur Y, Schattner A. Tumor necrosis factor- $\alpha$ -induced insulin resistance may mediate the hepatitis C virus-diabetes association. *Am J Gastroenterol*. 2003;98(12):2751–6.
48. Mitsuyoshi H, Itoh Y, Sumida Y, Minami M, Yasui K, Nakashima T. Evidence of oxidative stress as a cofactor in the development of insulin resistance in patients with chronic hepatitis C. *Hepatol Res*. 2008;38(4):348–53.
49. Bose SK, Shrivastava S, Meyer K, Ray RB, Ray R. Hepatitis C virus activates the mTOR/S6K1 signaling pathway in inhibiting IRS-1 function for insulin resistance. *J Virol*. 2012;86(11):6315–22.
50. Singhal A, Agrawal A, Ling J. Regulation of insulin resistance and type II diabetes by hepatitis C virus infection: a driver function of circulating miRNAs. *J Cell Mol Med*. 2018 Apr;22(4):2071–85.
51. Huang YW, Yang SS, Fu SC, Wang TC, Hsu CK, Chen DS, et al. Increased risk of cirrhosis and its decompensation in chronic

- hepatitis C patients with new-onset diabetes: a nationwide cohort study. *Hepatology*. 2014;60:807–14.
52. Elkrief L, Chouinard P, Bendersky N, Hajage D, Larroque B, Babany G, et al. Diabetes mellitus is an independent prognostic factor for major liver-related outcomes in patients with cirrhosis and chronic hepatitis C. *Hepatology*. 2014;60:823–31.
  53. Lai SW, Chen PC, Liao KF, Muo CH, Lin CC, Sung FC. Risk of hepatocellular carcinoma in diabetic patients and risk reduction associated with anti-diabetic therapy: a population-based cohort study. *Am J Gastroenterol*. 2012;107:46–52.
  54. Nkontchou G, Cosson E, Aout M, Mahmoudi A, Bourcier V, Charif I, et al. Impact of metformin on the prognosis of cirrhosis induced by viral hepatitis C in diabetic patients. *J Clin Endocrinol Metab*. 2011;96:2601–8.
  55. Delgado-Borrego A, Jordan SH, Negre B, Healey D, Lin W, Kamegaya Y. Reduction of insulin resistance with effective clearance of hepatitis C infection: results from the HALT-C trial. *Clin Gastroenterol Hepatol*. 2010;8(5):458–62.
  56. Aghemo A, Prati GM, Rumi MG, Soffredini R, D'Ambrosio R, Orsi E. Sustained virological response prevents the development of insulin resistance in patients with chronic hepatitis C. *Hepatology*. 2012;56(5):1681–7.
  57. Pavone P, Tieghi T, d'Ettorre G, Lichtner M, Marocco R, Mezzaroma I. Rapid decline of fasting glucose in HCV diabetic patients treated with direct-acting antiviral agents. *Clin Microbiol Infect*. 2016;22(5):462 e1–3.
  58. Fabrizio C, Procopio A, Scudeller L, Dell'Acqua R, Bruno G, Milano E. HCV and diabetes: towards a 'sustained' glycaemic improvement after treatment with DAAs? *Clin Microbiol Infect*. 2017;23(5):342–3.
  59. Ciancio A, Bosio R, Bo S, Pellegrini M, Sacco M, Vogliotti E, et al. Significant improvement of glycemic control in diabetic patients with HCV infection responding to direct-acting antiviral agents. *J Med Virol*. 2018 Feb;90(2):320–7.
  60. Drazilova S, Gazda J, Janicko M, Jarcuska P. Chronic hepatitis C association with diabetes mellitus and cardiovascular risk in the era of DAA therapy. *Can J Gastroenterol Hepatol*. 2018 Aug 13;2018: 6150861.
  61. Gastaldi G, Goossens N, Clément S, Negro F. Current level of evidence on causal association between hepatitis C virus and type 2 diabetes: a review. *J Adv Res*. 2017 Mar;8(2):149–59.
  62. Cacoub P, Desbois AC, Comarmond C, Saadoun D. Impact of sustained virological response on the extrahepatic manifestations of chronic hepatitis C: a meta-analysis. *Gut*. 2018;67(11):2025–34.
  63. Akbar DH, Siddique AM, Ahmed MM. Prevalence of Type-2 diabetes in patients with hepatitis C and B virus infection in Jeddah, Saudi Arabia. *Med Princ Pract*. 2002 Apr-Jun;11(2):82–5.
  64. Kabbaj N, Errabih I, Guédira M, El Atmani H, Benabed K, Al Hamany Z, et al. Hepatitis C and diabetes mellitus: effect of diabetes on the course of the liver disease. *Ann Endocrinol*. 2006 Jun;67(3):233–7.
  65. Antonelli A, Ferri C, Fallahi P, Sebastiani M, Nesti C, Barani L, et al. Type 2 diabetes in hepatitis C-related mixed cryoglobulinaemia patients. *Rheumatology (Oxford)*. 2004 Feb;43(2):238–40.
  66. Hunter SS, Gadallah A, Azawi MK, Doss W. Erectile dysfunction in patients with chronic hepatitis C virus infection. *Arab J Gastroenterol*. 2014 Mar;15(1):16–20.
  67. Abdelhamid AA, Sherief MH, Nemr NA, Hassoba HM, El-Sakka AI. Homocysteine, insulin-like growth factor one and oestrogen levels in patients with erectile dysfunction-associated chronic hepatitis C virus infection. *Andrologia*. 2018 Jul;31:e13116.
  68. Wang FP, Zhang PA, Yang XY. Relationship between sex hormones and RIG-I signaling in peripheral blood mononuclear cells of patients infected with hepatitis C virus. *Exp Ther Med*. 2017 Sep;14(3):2728–32.
  69. White DL, Tavakoli-Tabasi S, Kuzniarek J, Pascua R, Ramsey DJ, El-Serag HB. Higher serum testosterone is associated with increased risk of advanced hepatitis C-related liver disease in males. *Hepatology*. 2012;55:759–68.
  70. Magri A, Barbaglia MN, Foglia CZ, Boccato E, Burlone ME, Cole S, et al. 17 $\beta$ -estradiol inhibits hepatitis C virus mainly by interference with the release phase of its life cycle. *Liver Int*. 2017 May;37(5):669–77.
  71. Ahmed NH, El-Abaseri TB, El-Sayed HF, El-Serafi TI. Female sex hormones pattern and its relation to disease severity and treatment in pre- and postmenopausal patients with chronic hepatitis C virus (genotype 4) infection. *Int J Chronic Dis*. 2015;2015:927974.
  72. Soykan A, Boztaş H, Idilman R, Ozel ET, Tüzün AE, Ozden A, et al. Sexual dysfunctions in HCV patients and its correlations with psychological and biological variables. *Int J Impot Res*. 2005 Mar-Apr;17(2):175–9.
  73. Karaivazoglou K, Tsermpini EE, Assimakopoulos K, Triantos C. Sexual functioning in patients with chronic hepatitis C: a systematic review. *Eur J Gastroenterol Hepatol*. 2017 Nov;29(11):1197–205.
  74. Durazzo M, Premoli A, Di Bisceglie C, Bertagna A, Faga E, Biroli G, et al. Alterations of seminal and hormonal parameters: an extra-hepatic manifestation of HCV infection? *World J Gastroenterol*. 2006 May 21;12(19):3073–6.
  75. Hofny ER, Ali ME, Taha EA, Nafeh HM, Sayed DS, Abdel-Azeem HG, et al. Semen and hormonal parameters in men with chronic hepatitis C infection. *Fertil Steril*. 2011 Jun 30;95(8):2557–9.
  76. Hussein TM, Elneily D, Eid AA, Abou-ElKhier H. Assessment of antisperm antibodies in a sample of Egyptian patients with hepatitis C virus infection. *Andrologia*. 2017 Jun;49(5).
  77. Benvenga S, Guarneri F. Molecular mimicry and autoimmune thyroid disease. *Rev Endocr Metab Disord*. 2016 Dec;17(4):485–98.