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Review

Recovery of metabolic impairment in patients who cleared chronic hepatitis C infection after direct-acting antiviral therapy

Simone Lanini, Paola Scognamiglio*, Raffaella Pisapia, Claudia Minosse, Alessandro Agresta, Giuseppe Ippolito

National Institute for Infectious Diseases Lazzaro Spallanzani, IRCCS, Via Portuense 292, 00149 Rome, Italy

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ABSTRACT

Chronic hepatitis C (CHC) is a complex disease that can affect different metabolic processes, including glucose and lipid metabolic pathways, with a significant impact on the development of heart disease and stroke. Recent therapy with direct-acting antivirals (DAAs), beyond its high efficacy on CHC eradication, showed a beneficial impact on glucose and lipid metabolism. This review aimed to describe current evidence regarding the association between hepatitis C virus (HCV) infection and impairment of glucose and lipid metabolism and also discusses potential public-health implications in light of the new DAA therapies and their availability at a global level. The excellent safety profile and efficacy of DAAs offer an exceptional opportunity to control the HCV pandemic at a global level and represent an opportunity for developing an operational research framework aimed at investigating the complex dynamics between host, pathogen and therapy that lead to metabolic damage in subjects with infectious diseases.

1. Introduction

Hepatitis C virus (HCV) is a single-stranded RNA virus identified as the causative agent of chronic hepatitis C (CHC) in April 1989. It is estimated that ca. 71 million individuals worldwide are chronically infected with HCV. CHC is a major public-health issue and is associated with degenerative liver processes dominated by necroinflammatory damage leading to fibrosis, progressive decay of liver function, hepatocellular carcinoma and, eventually, death [1]. In many geographical settings, HCV-associated end-stage liver disease is the main reason for liver transplantation [2].

In addition to liver disease, CHC is associated with clinically significant metabolic alterations. Several studies have established that the prevalence of insulin resistance, accelerated atherosclerosis and metabolic syndrome are much higher among subjects with CHC than in the general population [3]. However, several authors have argued that the increased prevalence of metabolic conditions in patients with CHC is mainly due to non-causative associations (confounding) and that there is no evidence that metabolic alterations (e.g. higher fasting glucose levels and lower cholesterol and triglyceride levels) are actually associated with either metabolic syndrome [4] or with excess mortality [5].

The pathogenesis of metabolic alterations in patients with CHC is complex and depends on the dynamic interplay of several components such as the host innate metabolic profile [6], patient behaviour, co-infection with other pathogens (e.g. human immunodeficiency virous (HIV) [7] and tuberculosis (TB) [8]), genetic profile of the HCV (different genotypes are associated with differing impacts on metabolism), stage of liver disease [9] and exposure to previous host-directed anti-HCV therapies. Indeed, for nearly two decades, interferons (IFNs) have formed the basis for anti-HCV treatment. IFN-based regimens have significantly improved the life quality and expectancy of patients with CHC [10], however establishing whether these host-directed treatments could actually improve metabolic impairment due to HCV was difficult. In fact, the rate of HCV clearance was suboptimal, patients may need to receive multiple treatments, and IFNs may directly produce both reversible and permanent metabolic impairment [11–13]. The recent introduction of oral direct-acting antivirals (DAAs) has substantially changed the scenario of HCV therapy. DAAs have shown an excellent safety profile and extraordinary efficacy, with proportions of HCV clearance between 80–95% [14]. As DAA regimens do not have any absolute contraindications, there is broad consent that ambitious public-health programmes for optimal global control of CHC, including eradication, are currently possible [15].

This review aimed to describe current evidence regarding the association between HCV infection and impairment of glucose and lipid metabolism and also discusses potential public-health

* Corresponding author. Tel.: +39 06 5517 0936.
E-mail address: paola.scoganmiglio@inmi.it (P. Scognamiglio).

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implications in light of the new DAA therapies and their availability at a global level.

2. Hepatitis C virus and glucose metabolism

There is an extensive body of evidence that HCV infection may have a direct role in the development of insulin resistance. Epidemiological studies have long suggested that the prevalence of type 2 diabetes mellitus (T2DM) is much higher in subjects with CHC than in the general population, ranging between 13% and 67% according to liver fibrosis stage and time of infection [16–18]. However, several individual population studies based on cross-sectional analyses did not confirm a direct association between CHC and impairment of glucose metabolism, suggesting that most of the excess of risk of T2DM in patients with HCV infection was due to the confounding effect of other covariates including age, stage of liver disease and patient's body mass index (BMI) [5,6,19].

Nevertheless, these studies could have failed to establish a direct association between HCV infection and insulin resistance as a consequence of study design bias (cross-sectional studies cannot establish the sequence of events) and possibly lack external validity (these studies have been carried out on special populations and cannot be readily generalised).

In contrast, results from large meta-analyses have provided good evidence that HCV infection may actually have a direct role in the development of insulin resistance. In particular, a pivotal systematic review pooling data from 17 studies including 286 084 subjects found that the risk of T2DM was higher in patients with CHC than in uninfected people (odds ratio = 1.68, 95% confidence interval 1.15–2.45) [20]. Similar results have been reported by another independent meta-analysis of 34 observational studies carried out between 1998–2008 suggesting that the risk of developing T2DM was ca. 2 times higher in HCV-infected patients than in people without HCV infection including healthy controls and persons with either hepatitis B virus or HIV infection [21]. In addition, the direct association between HCV infection and an increased incidence of diabetes has been recently confirmed by a large, prospective, community-based study carried out on 21 559 adults followed-up for 20 years. In that study, 1917 incident diabetes cases were recorded with a cumulative risk of new-onset diabetes of ca. 17% in patients with CHC and 11% in uninfected subjects (hazard ratio = 1.31–2.02), suggesting that HCV infection preceded insulin resistance and thus may have a direct role in the pathogenesis of diabetes [22].

The hypothesis that HCV has a direct role in the pathogenesis of insulin resistance is also supported by evidence from basic science investigations. Experimental and clinical studies have suggested that HCV may interact with glucose metabolism through multiple mechanisms. HCV may directly inhibit the insulin-signalling pathway, with downregulation of glucose transporter 2, promotion of IRS-1 degradation through protein kinase B (Akt)/mammalian target of rapamycin (mTOR) activation, and suppression of phosphorylation of tyrosine on IRS-1. Moreover, HCV impairs phosphorylation of Akt leading to a reduction in insulin stimulation.

An important role has been ascribed to pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNFα), which suppress the action of insulin in the liver and peripheral tissue and oxidative stress promoted by HCV core protein (Fig. 1) [23–25].

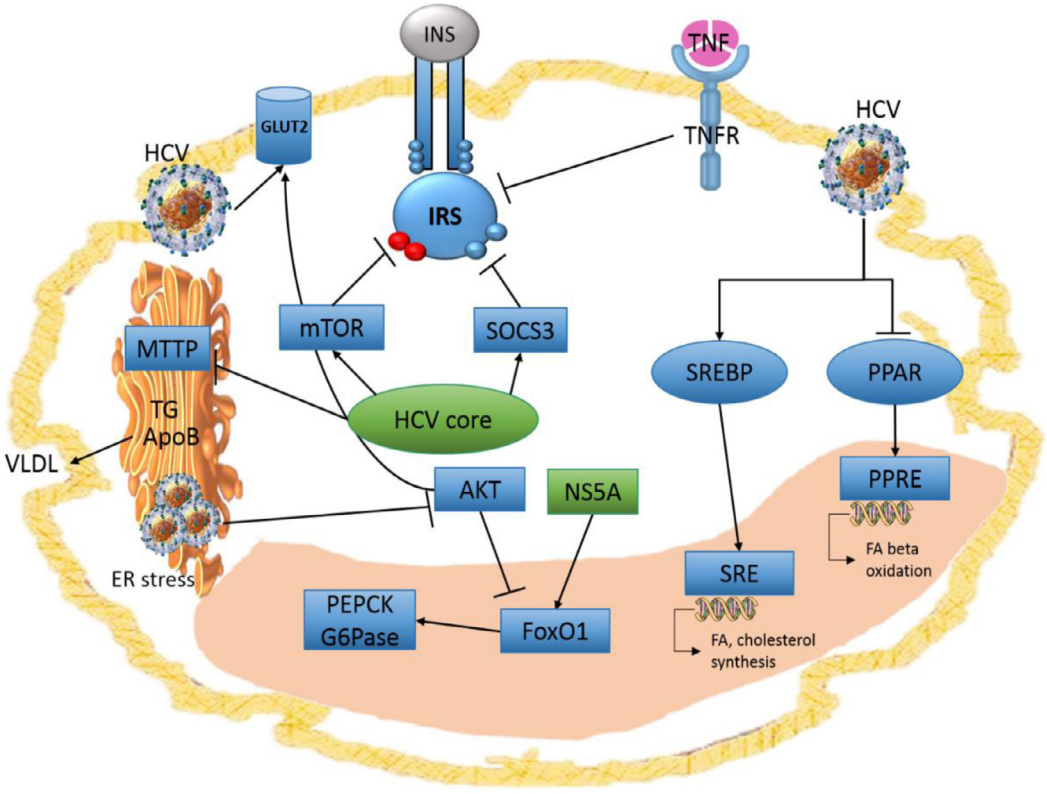

Fig. 1. Hepatitis C virus (HCV)-associated glucose and lipid metabolic changes. GLUT2, glucose transporter 2; INS, insulin; IRS, insulin receptor substrate; TNF, tumour necrosis factor; TNFR, tumour necrosis factor receptor; mTOR, mammalian target of rapamycin; SOCS3, suppressor of cytokine-signalling protein; AKT, protein kinase B (Akt); FoxO1, forkhead box protein O1, transcription factor; PEPCK, phosphoenolpyruvate carboxykinase; G6Pase, glucose-6-phosphatase; SREBP, sterol regulatory element-binding protein; SRE, sterol regulatory element; PPAR, peroxisome proliferator-activated receptor; PPRE, PPAR response element; NS5A, HCV non-structural protein 5A; MTTP, microsomal triglyceride transfer protein; VLDL, very-low-density lipoprotein cholesterol; ApoB, apolipoprotein B; TG, triglycerides; ER, endoplasmic reticulum; FA, fatty acid.

3. Hepatitis C virus and lipid metabolism

The association between HCV infection and dysregulation of lipid metabolism has been observed since long ago. The classical clinical features of patients with CHC are characterised by low serological levels of lipoproteins and total cholesterol, especially in patients with genotype 3 HCV [26], paralleled by increased parenchymal lipid accumulation (e.g. liver steatosis and accelerated atherosclerosis).

Clinical studies suggested that the prevalence of liver steatosis is much higher in patients with CHC than in HCV-non-infected subjects with other chronic liver diseases, including chronic hepatitis B, being between 40–86% and 20–50%, respectively [27,28]. In addition, different HCV genotypes are associated with different steatosis patterns, including steatosis associated with metabolic syndrome in patients infected with non-3 genotype (metabolic steatosis) and steatosis associated with high viral load and hypolipidaemia in patients infected with genotype 3 (viral steatosis). These different steatosis patterns could influence the natural history of CHC, as metabolic steatosis may increase hepatic damage and accelerate the fibrotic process [29–41].

Epidemiological studies have suggested that impairment of lipid metabolism in CHC could contribute to accelerated atherosclerosis and increase the risk of cardiovascular and cerebrovascular accidents [30]. Retrospective studies have shown that, after adjustment for confounding, the level of circulating HCV core protein is a strong independent predictor of carotid vascular alteration, including accelerated carotid plaque formation and intimal medial thickening [31,32]. These organic alterations demonstrate a direct association with liver steatosis and HCV-RNA load [33]. Indeed, the results of retrospective studies are supported by evidence from prospective studies [34,35] and meta-analysis [36] suggesting that CHC is associated with carotid atherosclerosis independent from classical risk factors and that HCV clearance after therapy is associated with a slow, although significant, improvement in the lipid profile.

The biological basis of the pathogenesis of lipid metabolism alteration in patients with CHC is strong. In fact, the HCV lifecycle is closely associated with the cholesterol and lipogenesis pathways in hepatocytes [37,38]. HCV circulates in the blood associated with lipoproteins, forming 'lipoviroparticles' that bind to hepatocytes via interaction with the low-density lipoprotein (LDL) receptor [39,40]. Indeed, recent molecular investigation suggested that HCV may affect host lipid metabolism in at least three ways: (i) enhancement of lipogenesis by upregulating de novo synthesis of fatty acids and cholesterol [fatty acid synthase, sterol regulatory element-binding protein (SREBP)]; (ii) impairment of lipoprotein degradation through mitochondrial lipid β-oxidation; and (iii) impairment of lipoprotein export by reducing microsomal triglyceride transfer protein (MTTP) (Fig. 1) [39].

4. Direct-acting antiviral therapy and metabolism

The complex interplay between HCV infection, the suboptimal safety profile of IFNs and the host baseline metabolic profile has previously resulted in contrasting evidence regarding the true effect of HCV clearance on individual metabolic impairment. Old studies suggested that clearance of HCV following IFN-based therapy could have even resulted in a worsening lipid metabolic profile and cardiovascular risk. However, in recent years, treatment of chronic HCV infection has dramatically improved with the development of IFN-free regimens based on DAAs. These drugs, which specifically target non-structural viral proteins, have highly improved sustained virologic response (SVR) rates of >90% with a shortened treatment duration and reduced side effects; thus, CHC has become a curable disease in the majority of treated patients, including those previously considered as difficult to treat [16]. Moreover, recent evidence has suggested that DAA treatment is associated with improvement in metabolic impairment and that potential concerns regarding the toxicity of long-term IFNs on the cardiovascular system do not apply to DAAs [13,33].

A retrospective study suggested that clearance of HCV with sofosbuvir-containing regimens resulted in a significant drop in haemoglobin A1c (HbA1C) and an increase in LDL and triglycerides up to 6 months post-HCV eradication. Although not statistically significant, patients with a history of diabetes tended to have a higher drop in HbA1C than those without diabetes, and patients with a high pre-treatment viral load tended to have a higher drop in HbA1C [40].

Consistent with these results, we carried out an analysis of 300 patients with CHC to describe the temporal kinetics of fasting glucose level during and after DAA therapy. In this study, we found strong evidence that blood glucose levels significantly dropped in patients with diabetes who cleared HCV infection. Most of the observed variation occurred early in time and in temporal coincidence with HCV clearance. Furthermore, the metabolic improvement was persistent with a reduction of average fasting glucose level for >1 year after the end of therapy, rejecting the hypothesis that DAAs may affect per se on blood glucose levels (Lanini S, unpublished data). Similar results were reported in other studies suggesting that a reduction of fasting glucose levels after HCV clearance was independent from HCV genotype, BMI and the DAA regimen used [41,42] and that it was associated with a reduction in the use of insulin in diabetic patients [43,44].

In addition to the improvement in insulin resistance, there are good reasons to believe that HCV-associated hypolipidaemia can be completely reversed following viral clearance achieved with DAAs.

Several studies provided evidence that lipoprotein levels and liver lipid accumulation tended to normalise after the initiation of combination therapy including with sofosbuvir/ribavirin [12,45], sofosbuvir/ledipasvir [46], asunaprevir/daclatasvir [47] and grazoprevir/elbasvir [48]. These modifications appear to be associated with significant improvement of steatosis and atherogenesis [30–49].

The beneficial effect of HCV clearance on the metabolic profile was also observed in complex patients such as those with CHC who received a liver transplant. In these subjects, eradication of recurrent HCV infection by DAA therapy showed a beneficial impact on glucose and lipid metabolism leading to a reduction in the need for treatment of diabetes and hypertension by 38% and 22% from baseline, respectively [49].

However, some authors observed that elevated alanine aminotransferase (ALT) levels may persist in from 10% up to 30% of subjects after SVR, suggesting that liver damage may persist following HCV clearance as a consequence of behavioural and constitutional factors. Persistent elevated ALT levels following SVR are associated with male sex, advanced liver disease and markers for liver steatosis, highlighting that liver disease in patients with CHC may have a multifactorial aetiology [50,51]. Prospective observational studies are needed to define the interplay between metabolic impairment and potential progression of liver damage following SVR.

5. Future perspectives

Metabolic impairments are emerging causes of mortality and morbidity at a global level. In particular, T2DM has attained the status of a global pandemic, spreading from rich industrialised countries to middle- and low-income countries in Asia, Latin America and Africa. In special geographical settings, such as urban areas of India, insulin resistance affects >25% of the population whilst overt T2DM has a prevalence exceeding 10% [52]. Recent evidence suggests that there is a complex interplay between chronic and

recurrent infections and metabolic diseases resulting from the combined deleterious effects of pathogens and anti-infective therapies on metabolic homeostasis. Recent studies provided evidence that co-clustering of metabolic disorders with infectious diseases such as HIV/AIDS [53,54], TB [55] and malaria [56] already represents a significant public-health issue in developing countries.

CHC is a complex disease affecting different host biological structures and metabolic processes, including glucose and lipid metabolic pathways. According to recent estimates, ca. 47 million individuals worldwide may have overt T2DM as a consequence of HCV infection and there is widespread agreement that HCV may have a negative impact on the development of heart disease and stroke [4].

Therapy with DAAs offers an exceptional opportunity to control the HCV pandemic at a global level and also represents a unique opportunity to develop an operational research framework aimed at investigating the complex dynamics between host, pathogen and therapy that lead to metabolic damage in subject with infectious diseases. DAAs are orally-administered dugs with an exception efficacy and safety profile. This makes it possible to provide effective therapy to all patients all over the world regardless of the stage of liver disease [10]. At present there is a need to confirm whether eradication of HCV may also counter (or even revert) metabolic impairments and improve patients' clinical outcomes in the long term. In affluent industrial countries, national guidelines have already implemented evidence on the positive effect of DAAs on metabolism into clinical practice by recommending immediate treatment for all subjects and strict monitoring after therapy for those with extrahepatic conditions, including metabolic impairment and high-risk cardiovascular diseases. In these settings, implementation of an operational research framework directly supported by local health authorities will be pivotal to assess and quantify the actual impact of anti-HCV treatment on extrahepatic conditions [14]. Besides, there is a need to expand access to DAAs to all subject with CHC despite the stage of liver disease in developing countries and in particular in those geographical settings with a high prevalence of CHC and metabolic diseases such as T2DM.

6. Conclusions

CHC is now a curable condition. New therapies with DAAs promise to clear infection in most patients, including those previously considered difficult to treat. In addition, the optimal safety profile of DAA regimens makes it possible to also treat frail patients with several co-morbidities and, in fact, previous concern regarding IFN therapy, including increased cardiovascular risk, permanent effects on metabolism and acute liver decompensation, do not apply to IFN-free regimens. Given the optimal safety profile and exceptional efficacy, therapy with DAAs represents a unique opportunity to study metabolic impairment in patients with HCV chronic and recurrent infection. The optimal environment for these investigations is, in our opinion, composed of a solid operational research framework implemented within solid local networks supported by local health authorities in developed countries [14] and/or within internationally-funded programmes in resource-limited settings [57]. This approach could eventually be expanded to other infectious diseases that have clinically significant metabolic implications.

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Competing interest

None declared.

Ethical approval

Not required.

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