Metabolic disorders and chronic viral disease: The case of HIV and HCV

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Abstract

The importance of metabolic disorders in the pathophysiology of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections is becoming increasingly apparent. Metabolic anomalies, with their potential for multiple-organ involvement, are to be expected, given the chronic nature of these diseases, and the intracellular dysregulation associated with them. Not only have the endocrine and cytokine metabolic anomalies seen in HIV and HCV infections been linked with the metabolic syndrome, but they also appear to have some pathways in common. Studying the differences and similarities between these metabolic anomalies may add to our understanding of HIV and HCV infection, and provide guidance on how to treat these chronic diseases. This review highlights the principal underlying factors for metabolic disorders in these chronic viral diseases—namely insulin resistance and liver damage. Both the chronic viral state itself and the host immune response give rise to glucose and lipid metabolic disorders that, in turn, are risk factors for hepatic damage. The various interactions between HIV and/or HCV with insulin resistance, type 2 diabetes, steatosis and fibrogenesis should be considered when determining the treatment and long-term follow-up of patients. Recent data indicate that HCV clearance improves insulin resistance and hepatic function in HCV-infected patients treated with interferon with or without ribavirin.

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Résumé

Troubles métaboliques et maladies virales chroniques : qu'en est-il du VIH et du VHC ?

L'importance des anomalies métaboliques dans la physiopathologie des infections par le virus de l’immunodéficience humaine (VIH) et le virus de l’hépatite virale C (VHC) est aujourd’hui de plus en plus reconnue. En effet, du fait des dérèglements cellulaires qui accompagnent la persistance et la chronicité de ces infections virales, la survenue d’anomalies métaboliques est prévisible et concerne plusieurs tissus. De plus, les anomalies endocrines et cytokiniques qui accompagnent les infections à VIH et VHC mettent en jeu des voies en partie communes qui les rapprochent toutes deux du syndrome métabolique. L’analyse de ces troubles métaboliques pourrait aider à mieux appréhender les infections à VIH et VHC et leur prise en charge médicale. Cette revue souligne le rôle prépondérant de l’insulino-résistance et des lésions hépatiques parmi les facteurs qui conduisent à ces troubles: les virus eux-mêmes, mais aussi la réponse immune induite chez l’hôte, entraînent des troubles du métabolisme lipidique et glucidique qui sont à leur tour facteurs de risque de lésions tissulaires hépatiques. La prise en charge thérapeutique des patients au long cours doit prendre en compte les différentes interactions entre VIH, VHC et insulino-résistance ou diabète de type 2, stéatose et fibrogenèse. Ainsi, les données récentes indiquent que l’éradication virale améliore l’insulino-résistance et la fonction hépatique chez des patients porteurs du VHC et traités par interféron, avec ou sans ribavirin.

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1. Introduction

The persistent chronic characteristics of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections result in metabolic anomalies that can contribute to, complicate or themselves be associated with a metabolic syndrome. In HIV, the relationship between metabolic anomalies and individual drugs, as well as different classes of antiretroviral drug treatments, has been well described and reviewed [1–4]. Therefore, our objective is not to further review these associations, but rather to set more light on the factors associated with the intracellular dysregulation caused by the viral infection itself and on the common pathways between HIV and HCV, as well as on the consequences that result in insulin resistance and liver damage. Nevertheless, as a consequence of antiretroviral treatment, some HIV-infected patients present with lipodystrophy that may be difficult to reverse, and might be responsible for insulin resistance and metabolic disorders leading to liver damage.

2. Defining the metabolic syndrome

The metabolic syndrome comprises a constellation of interrelated metabolic risk factors for cardiovascular disease (CVD) and type 2 diabetes mellitus [5,6]. The specific characteristics of this syndrome vary according to the definition used [7–11]. Insulin resistance is a key component of the World Health Organization (WHO) and European Group for the Study of Insulin Resistance (EGIR) classifications [7,8]. However, in daily clinical practice, direct measurement of this risk factor is complicated. For this reason, these classifications tend to be more useful as research tools. The National Cholesterol Education Program–Adult Treatment Panel III (NCEP–ATP III) guidelines define the metabolic syndrome as the presence of at least three out of five risk factors: abdominal obesity; elevated blood pressure; and elevated fasting glucose; elevated serum triglycerides; and low levels of high-density lipoprotein (HDL) cholesterol. Thus, this definition can readily be used to identify the individuals at risk who require a change in lifestyle and/or therapeutic intervention.

Although differences in criteria and definitions make it difficult to compare studies, older age, a high body mass index (BMI) and insulin resistance are associated with an increased risk for metabolic syndrome [12–14]. Currently, the greatest emphasis is placed on how the risk factors of the metabolic syndrome relate to atherogenesis and CVD [15]. However, all such risk factors, whatever their origin are also associated with hepatic metabolic dysfunction leading to steatosis, with steatohepatitis and other complications such as fibrosis and hepatocellular carcinoma as possible sequelae.

3. Pathophysiology of the metabolic syndrome

As described above, obesity and insulin resistance are strong risk factors for the metabolic syndrome. In obese patients, excess in abdominal body fat, predominantly seen as an increased waist circumference, is deleterious, whereas peripheral body fat is neutral or even protective against metabolic anomalies [16–18]. Indeed, central body fat is partly subcutaneous, but also visceral, and an accumulation of visceral adipose tissue is believed to increase free fatty acid (FFA) influx to the liver via the splanchnic circulation [19]. In addition, visceral adipose tissue probably secretes a number of cytokines and adipokines that act on the liver. Subcutaneous fat also releases lipolytic products and adipokines into the systemic circulation, and even if the effects on the liver are less direct—which they are thought to be—such fat deposition is also considered deleterious to metabolic parameters.

The underlying mechanisms of insulin resistance have mostly already been elucidated. Glucose intolerance results from an impaired ability of insulin to:

- suppress hepatic glucose production;
- mediate glucose uptake and metabolism by insulin-sensitive tissues (mainly muscle).

In particular, the association of proinflammatory cytokines with the metabolic syndrome is well established [19]. Interleukin-6 (IL-6), resistin and tumour necrosis factor-α (TNF-α) are overproduced by the expanded adipose-tissue mass and the excessive number of monocyte-derived macrophages. Together with a chronic, low-grade inflammatory state, these factors induce insulin resistance in adipose, liver and muscle tissues.

On the other hand, adiponectin, an anti-inflammatory cytokine secreted mainly by adipocytes, may also be involved. This substance enhances insulin sensitivity and inhibits several steps of the inflammatory pathway [20–22]. Adiponectin controls glycaemia by inhibiting the expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production in the liver [23]. In muscles, adiponectin raises glucose uptake and enhances FFA oxidation [24,25]. Low adiponectin levels have been shown to be consistently associated with nonalcoholic steatohepatitis (NASH) [26].

Nonalcoholic fatty liver disease (NAFLD) is another common feature of the metabolic syndrome, and may lead to NASH [27,28], which links triglyceride accumulation to the development of chronic inflammation and hepatocyte alterations. It has been proposed that insulin resistance leads to the initial deposition of lipids in hepatocytes, resulting in steatosis. In the metabolic syndrome, insulin resistance is one important cause of the overabundance of circulating FFA released by adipose tissue through the activation of adipocyte hormone-sensitive lipase. It makes the liver vulnerable to a second “hit” or injury, leading to further damage [29]. However, the mechanisms involved in inflammation and fibrosis in this second hit have yet to be fully elucidated.

Increased liver triglycerides can result from increased triglyceride synthesis or from decreased fatty acid degradation, with different underlying mechanisms:

- excess lipid content in the diet;
- altered dietary fatty acid composition;
• increased de novo lipogenesis (activation of the transcription factor sterol regulatory element-binding protein-1 [SREBP-1] by insulin);
• increased FFA influx to the liver from adipose tissue;
• increased levels of remnant lipoproteins (chylomicrons and very low-density lipoprotein [VLDL] rich in triglycerides) due to decreased clearance at the adipose tissue level;
• increased hepatic triglyceride synthesis with increased production of apo-B-containing VLDL [30].

In addition, circulating lipid alterations are observed, such as [31,32]:
• changes in HDL composition and metabolism, causing a reduction in the cholesteryl ester content of the lipoprotein core, thereby increasing plasma HDL clearance;
• modifications to the composition of low-density lipoprotein (LDL), resulting in a predominance of small, dense LDL with an increased potential to cause atherogenesis.

These alterations are attributable to a relative depletion of cholesterol and phospholipids with or without a change in LDL triglyceride content [33,34].

An excess of FFA modifies the downstream signalling in insulin-sensitive tissues, resulting in further insulin resistance. In the muscle, the activation of an atypical form of protein kinase C leads to the phosphorylation of insulin receptor substrate-1 (IRS-1) on serine residues, resulting in insulin resistance [35]. In the liver, a defect in IRS-1 phosphorylation has also been described in an animal model as a consequence of a high-fat diet leading to steatosis [36].

4. Metabolic syndrome and metabolic anomalies in HIV and HCV infections

Abnormalities in metabolism have been identified in patients with HIV or HCV infection [37–41]. In HIV-infected patients, dyslipidaemia, glucose metabolic anomalies and lipodystrophy appear to be key features [37]. Components of the metabolic syndrome, such as obesity or diabetes, are frequently present in HCV-infected patients, and have been described as independent risk factors for liver fibrosis [38–40].

Abnormalities in hormone and cytokine levels, along with alterations in their metabolism, have long been established in HIV infection. However, the advent of highly active antiretroviral therapy (HAART) has been accompanied by a rise in the prevalence of another complex condition generally known as “HIV-associated lipodystrophy” [37,42]. In addition, certain metabolic anomalies are currently recognized as being extrahepatic manifestations of chronic HCV infection. However, more recent evidence has raised questions over the possible role of metabolic factors in the severity of the disease as well as their effect on treatment response.

Studying the differences and similarities in the metabolic abnormalities associated with these two viral infections may well add to our understanding of how to treat these chronic diseases.

5. Chronic viral infection, immune disorders and liver damage

Some chronic infectious states disturb lipid metabolism by disrupting common metabolic pathways: hypertriglyceridaemia and low plasma cholesterol levels have been historically described as resulting from bacterial, parasitic and viral infections [43]. In response to infection, cytokines such as TNF-α, IL-1, IL-6 and interferons (IFN) mediate the host immune response [43]. Consequently, lipoprotein lipase activity is reduced and hepatic lipid synthesis stimulated, thereby provoking hypertriglyceridaemia. Although now often associated with therapy, lipid and glucose metabolic disorders were described in HIV-infected patients even before the HAART era. Various mechanisms have been proposed to explain the therapy-independent metabolic disorders at the onset of chronic HIV infection.

6. Demographic factors and HIV infection

The effects of demographic factors and HIV disease itself on serum lipids and glucose homoeostasis have been demonstrated in large and diverse HIV-infected populations [44,45]. A high prevalence of CVD risk factors is frequently described, although the overall increased incidence of CVD itself is relatively limited. In the SMART study, patients with CD4-count-guided interruption of antiretroviral treatment experienced a significantly increased risk of CVD compared with patients whose treatment was sustained, suggesting a role for HIV infection in CVD that is independent of treatment [46]. In another study of HIV-infected patients [47], total cholesterol levels prior to the initiation of HAART were lower, while triglyceride levels were higher than normal. During treatment, HDL cholesterol remained significantly lower than normal.

Although CVD risk factors appear to be generally worse in HIV-infected patients than in the general population, this does not appear to translate to an increased incidence of metabolic syndrome. Its incidence was compared between a cohort of HIV-infected adult patients and the general US population (National Health and Nutrition Examination Survey [NHANES] 1999–2002 cohort) [48]. After adjusting for demographics, physical activity and diet, the prevalence of the metabolic syndrome was lower in HIV-infected patients than in the general US population, whether they were treated with HAART or not. Indeed, in the general population, waist circumference is associated with increased fat at both subcutaneous and visceral levels. The prevalence of obesity is lower in HIV-infected patients in Europe. In this population, the most prevalent factor responsible for the diagnosis of the metabolic syndrome was dyslipidaemia (involving triglycerides and HDL cholesterol). Finally, recent elevation of HIV viral load, but not absolute viral load, was found to predict the risk for the metabolic syndrome. These results were corroborated by a prospective, cross-sectional analysis that revealed a high prevalence of the metabolic syndrome in HIV-infected patients (25.6%), but which was no higher than that of a matched sample from the general US population (NHANES 2001–2002 cohort, 26.5%) [49]. However, because the waist
parameter is less appropriate for evaluating the metabolic risk in an HIV-infected population, using definitions of the metabolic syndrome adapted for the general population could lead to underestimation of the metabolic risk in some patients.

Thus, it appears that HIV-infected patients may be affected by the current “epidemic” of the metabolic syndrome and its related complications as seen in the general population, although the diagnosis is less obvious. Data from a cohort of 50 men in the prospective Multicenter AIDS Cohort Study who later initiated HAART showed notable declines in mean total, HDL and LDL cholesterol levels from the time of seroconversion [50]. Twelve years later, the increase in total cholesterol levels was consistent with expected age-related changes, irrespective of HIV or therapeutic status. Furthermore, subsequent HAART interventions resulted in an increase in both total and LDL cholesterol, but had a minimal effect on HDL cholesterol levels. Although triglyceride levels were not determined, these results suggest that a significant proportion of the observed rise in total and LDL cholesterol could represent a return to pre-seroconversion levels.

7. Chronic viral disease and liver-driven lipid disorders in HIV infection

The metabolic disturbances related to HIV were initially described as part of the AIDS-related wasting syndrome [51,52]. However, these disturbances were also found in HIV-infected patients with normal body weight and CD4 cell counts [53]. In a study comparing healthy volunteers with HIV-infected patients who were either asymptomatic or experiencing weight loss, HIV infection was characterized by abnormal fat anabolism early in the natural history of the infection. This suggests that abnormal hepatic synthesis may be caused by fundamental pathogenic mechanisms linked to HIV itself.

Several such mechanisms have been suggested [53]. Ongoing lipogenesis may impair hepatic ketogenesis in favour of FFA esterification, consistent with elevated serum triglyceride levels. In addition, as part of the wasting syndrome, the metabolic “cost” of lipogenesis preceding oxidation could be contributing to a hypermetabolic state. In both fasted and fed states, the rate of de novo lipogenesis was three to four fold higher in HIV-infected patients experiencing weight loss than in controls [53]. “Carbohydrate disposal” into lipogenesis may, therefore, contribute to amino acid wasting in the event of inadequate protein and carbohydrate disposal” into lipogenesis may, therefore, contribute to amino acid wasting in the event of inadequate protein and calorie intakes. However, impaired VLDL clearance may partly explain hypertriglyceridaemia, but not wasting or lipid-stores depletion in the muscles. The increased de novo lipogenesis found in HIV-infected patients with neither weight loss nor low CD4 cell counts suggests that asymptomatic HIV infection is characterized by activation of the immune response rather than by a truly latent viral state [53].

8. The proinflammatory state and its consequences in HIV infection

Early in the HIV epidemic and before the introduction of HAART, AIDS was reported to be frequently accompanied by altered lipid levels that were related to circulating IFN-α levels, a cytokine with levels known to be elevated in this setting [53]. A study comparing male AIDS patients with age-matched HIV-infected patients and controls reported significantly higher triglyceride levels in AIDS patients [47]. The clearance of triglyceride-rich particles was significantly prolonged in AIDS patients and was already slower in HIV-infected patients compared with controls; it was also correlated with reduced enzymes involved in triglyceride clearance, and increased de novo hepatic lipogenesis and VLDL production. Striking reductions in cholesterol, apolipoproteins and HDL cholesterol levels were found in HIV-infected patients who had not yet developed hypertriglyceridaemia. This suggests an early host response to HIV prior to the development of triglyceride metabolic disorders in the course of HIV infection. In this study, TNF-α levels were not found to be markedly elevated. Therefore, the general population may be more sensitive to the cholesterol-lowering effect of IFN-α than its triglyceride-raising impact. However, the pulsatile release and rapid clearance of TNF-α may have contributed to inaccurate measurements. For this reason, TNF-α-stimulated acute-phase proteins were also measured as surrogate parameters revealing that C-reactive protein was elevated in AIDS patients, and that haptoglobin levels also remained high for longer periods in AIDS and HIV-infected patients versus controls. Finally, cytokine-induced hyperlipidaemia was not inevitably linked to wasting, as suggested by the stable body weight of many HIV and AIDS patients, despite the major lipid metabolic disturbances observed during the study.

9. Glucose metabolism disorders in HIV infection

While increased insulin sensitivity has been reported in one study of HIV-infected patients in the pre-HAART era [54], this topic was poorly investigated at that time. Also, lipodystrophy has been strongly associated with the antiretroviral treatment. However, recent studies indicate that some viral proteins may impede adipocyte differentiation through decreased peroxisome proliferator-activated receptor-gamma (PPARγ) expression, and contribute to insulin resistance, suggesting that HIV infection could also play a role in lipodystrophy [55]. This is also suggested by data obtained from adipose tissue samples from naive HIV-infected patients revealing a strong decrease in adipogenic factors such as PPARγ, as found in samples from lipodystrophic patients undergoing ART [56]. Therefore, fat loss may not only be due to the treatment, but also to the viral infection itself. Studies of human genetic lipodystrophy have clearly outlined the insulin resistance associated with lipoatrophy. Taken altogether, these data suggest a role for adipose-tissue redistribution in insulin resistance, probably through the altered secretion of cytokines and adipokines, and the increased production of FFA by lipodystrophic fat tissue [42].

Indeed, in the HIV-associated lipodystrophy syndrome, it appears that the observed insulin resistance differs from that of type 2 diabetes and obesity: the clinical and biological characteristics of this syndrome are more like those of rare forms of acquired and congenital lipodystrophy, with a loss of trunk and limb fat, insulin resistance and increased FFA levels [57]. Com-
pared with healthy volunteers and HIV-infected nondiabetic patients without lipodystrophy, insulin sensitivity was reduced two fold in HIV-infected lipodystrophy patients, and correlated with a reported reduction in limb fat [57]. Furthermore, although HIV disease was well controlled in these patients, TNF-α receptor levels were elevated while adiponectin levels were decreased and strongly correlated with insulin resistance [58]. This suggests that inflammation may be contributing to the pathophysiology of lipodystrophy and insulin resistance in HIV infection.

10. Glucose metabolism disorders in HCV infection

Supporting the hypothesis that chronic viral diseases are a cause of metabolic syndrome per se, experimental and clinical data suggest that chronic HCV infection is a risk factor for the development of glucose intolerance and diabetes [59–62].

Cross-sectional surveys have shown a high prevalence of HCV infection in type 2 diabetic patients, ranging from 4.2 to 11.5%, compared with rates in controls ranging from 0.1 to 2.5% [59,60,63,64]. A high prevalence of HCV infection was found in a prospective cohort of type 2 diabetic patients compared with blood donors matched for recognized risk factors for HCV [59]. In diabetic HCV-infected patients, abnormal liver enzymes were observed in 72% of cases, suggesting a combination of cytolysis and cholestasis. Also, in transfused patients for whom data were available, HCV infection appears to have been acquired long before the development of diabetes.

On the other hand, the prevalence of type 2 diabetes is higher in patients with chronic HCV infection, ranging from 21 to 50%, compared with patients with other chronic liver diseases, whose rates range from 9 to 12% and are independent of the stage of fibrosis [60,65–67]. In the liver-disease cohort, diabetes was found in 21% of HCV-infected patients versus 12% of hepatitis B virus (HBV)-infected patients. In this cohort, age and HCV infection were the only independent risk factors for diabetes.

A US multicentre, prospective, case-cohort analysis of the Atherosclerosis Risk in Communities (ARIC) Study— involving patients with similar diabetes risk factors, but who were HCV-negative—also confirmed that HCV infection preceded the onset of diabetes [61]. HCV infection may have modified the effects of age and BMI on the risk of diabetes. Indeed, obese (BMI above 30 kg/m²) HCV-infected patients displayed significantly higher insulin levels and insulin resistance at baseline compared with HCV-negative obese individuals regardless of diabetes status. It has also been shown that HCV infection is a risk factor for diabetes mellitus early after liver transplantation [68,69]. In another large cohort of nondiabetic HCV-infected patients, the prevalence of insulin resistance assessed by the homeostasis model assessment (HOMA) index was significantly higher in HCV-infected patients compared with HBV-infected patients matched for age, gender and fibrosis stage (35% versus 5%, P < 0.001) [62].

Clinical data suggest the presence of an HCV-induced insulin resistance in which:

- the degree of insulin resistance is related to the level of viremia [62];
- insulin resistance is reversed in patients with a sustained virological response [70];
- insulin resistance appears to be genotype-specific (genotype 1 or 4) [71,72]. This latter result was confirmed by experimental data showing that insulin signalling inhibition was genotype-specific in HCV core protein-transfected cells with different HCV genotype strains [73].

Several pathogenic mechanisms may be involved in the effect of HCV on insulin resistance [59,61,74,75]. The primary underlying mechanism is probably inflammatory as there is a well-described relationship between TNF-α and IL-6 and the risk of developing insulin resistance and type 2 diabetes in both diabetic and nondiabetic patients. Nondiabetic HCV-infected patients have been shown to have higher insulin resistance than patients with other chronic liver diseases, and this was associated with activation of the TNF-α system and high serum IL-6 levels. The TNF-α effect may be related to the immune response mediated by T-helper 1 lymphocytes. Indeed, these cells secrete IFN-γ, which enhances the production of TNF-α and its receptors by macrophages (in the circulation and in Kupffer cells). A transgenic mouse model has strongly suggested that elevated intrahepatic TNF-α levels play a major role in the development of HCV-related insulin resistance by suppressing the insulin-induced tyrosine phosphorylation of IRS-1 through a core protein-related mechanism.

In patients with chronic HCV infection, intrahepatic insulin-stimulated IRS-1 Tyr-phosphorylation is reduced, and associated with insulin-stimulated PI3-kinase activity reduction and insulin-stimulated Akt phosphorylation impairment [76]. In patients with a sustained virological response, intrahepatic IRS-1 expression increased after clearance of HCV [77]. In transgenic mice, HCV core protein induced insulin resistance prior to the development of liver steatosis, and the administration of anti-TNF-α antibodies restored insulin sensitivity [78]. Also, hepatocytes produce IL-6, which promotes insulin resistance by inhibiting transcription of the glucose transporter 4, IRS-1 and PPAR. Also, IL-6 levels have been found to be higher in HCV-infected patients than in non infected individuals [79,80], and correlate with the histological severity of liver inflammation [79]. The link between inflammation and insulin resistance in chronic hepatitis C may be the suppressor of cytokine signalling (SOCS)-3 protein, which is upregulated, and associated with IRS-1 and IRS-2 decreases in HCV core protein-transfected cells [77].

Another underlying mechanism is hepatic steatosis (described further in the next section), which has been reported more frequently in HCV than in HBV infection [81], and in association with HCV genotype-3 infection and visceral obesity [82]. However, while insulin resistance is associated with steatosis in patients infected with genotypes other than genotype 3, the lack of association of insulin resistance with genotype-3-related steatosis indirectly suggests that insulin resistance is the cause, rather than the consequence, of steatosis in chronic HCV infection [83,84]. Iron overload associated with
chronic HCV infection may be another mechanism of insulin resistance. However, the lack of relationship between the degree of insulin resistance, assessed by HOMA, and intrahepatic iron concentration suggests that iron overload plays a minor role in insulin resistance in patients with chronic HCV infection [83].

Furthermore, chronic HCV infection is, to some extent, an autoimmune disease. The triggering of β-cell autoimmunity related to HCV antigens or immune complexes may induce the autodestruction of endocrine pancreatic tissue; however, the diabetes described in HCV-infected patients tends to be type 2 [60], and a clear association has yet to be demonstrated.

11. Steatosis in viral infections of the liver

Liver injury can be induced by insulin resistance in HIV patients. NASH is common in HIV-infected patients, whether or not they are coinfected with HBV or HCV. In a US veterans study, NASH was reported in 30% of patients, and was strongly correlated with BMI and waist circumference, and weakly correlated with stavudine use [85]. HIV-infected patients treated with HAART who had chronic alanine aminotransferase elevations of unknown origin were also found to be at increased risk of liver lesions, with predominantly histological patterns of NASH related to insulin resistance [86]. A larger study of 1028 HIV-infected patients found advanced liver fibrosis in only 2% of patients, but this was correlated with prolonged exposure to didanosine and/or stavudine and high plasma glucose levels [87].

Transcription factors regulating lipid metabolism (such as PPARγ1, PPARγ2 and SREBP-1) could play a major role in the pathogenesis of NAFLD with NASH in HIV-infected patients. The expression of these factors was evaluated in HIV-infected lipodystrophy patients (with or without insulin resistance), non-HIV patients with NAFLD and non-HIV/non-NAFLD control patients [88]. Compared with NAFLD or the control patients, SREBP-1 expression was significantly higher only in HIV infected and insulin-resistant patients. Steatosis was also associated with fibrosis, and decreased expression of PPARγ1 and PPARγ2. The authors postulated that altered expression of SREBP-1 and PPARγ could play a role in the pathogenesis of steatosis and fibroproliferative changes in insulin-resistant lipodystrophy patients. NASH is also characterized by ongoing inflammation associated with overexpression of proinflammatory cytokines such as TNF-α [89], which may reduce PPARγ expression. On the other hand, no relationship was observed between the degree of steatosis and fibrosis, and either HIV severity or type of HAART [88]. These results may suggest that insulin-resistant lipodystrophy patients can develop NASH in the absence of alcohol abuse or coinfection.

12. Liver injury induced by insulin resistance in HCV infection

The importance of liver injury in the onset of insulin resistance and diabetes has been more extensively described in HCV than in HIV. A correlation between insulin resistance, and steatosis and fibrosis progression, was established in a retrospective study in 141 non-diabetic and untreated patients with biopsy-proven noncirrhotic chronic HCV monoinfection [83]. Other authors have also suggested a correlation between cirrhosis and an increased risk of glucose intolerance or diabetes in HCV-infected patients [60,61]. In addition, the pathophysiology of steatosis in HCV differs as a function of the viral genotype [82,90].

In patients infected with HCV non genotype 3, insulin resistance and obesity are the cause, rather than the result, of steatosis which, in turn, accelerates progression of fibrosis [91,92]. One possible mechanism is that the virus itself impairs IRS-1 signalling, downregulated by an excess of FFA. On the other hand, in genotype-3 HCV infection, the degree of steatosis is strongly correlated only to the viral load [82], suggesting that the virus itself may alter FFA metabolism and/or FFA export by hepatocytes, with steatosis as a direct consequence. These results are supported by evidence that liver steatosis is correlated with intrahepatic HCV replication in HCV infection [93].

Elevated serum glucose was also shown to be independently associated with significant fibrosis in HCV-infected patients [39]. Patients with hyperglycaemia had higher histological fibrosis stages and progression rates, and had steatosis more frequently than patients with normal serum glucose. Possible mechanisms by which high serum glucose may contribute to fibrogenesis are:

- hyperglycaemia, which results in the increased formation and deposition of advanced glycation end products [94] that interact with receptors in hepatic stellate cells, the main source of collagen in the liver [95];
- elevated glucose levels, which induce profibrogenic cytokine expression in hepatic stellate cells (connective tissue growth factor, for example) [96];
- chronic hyperglycaemia and circulating soluble advanced glycation end products, which increase oxidative stress by generating free radicals [97] that activate stress-responsive signalling pathways [98] which, in turn, induce key inflammatory cytokines (such as TNF-α and IL-6) [99].

Alternatively, insulin resistance rather than hyperglycaemia may be linked to necroinflammatory lesions and, hence, fibrogenesis. A correlation between insulin resistance and fibrosis progression was demonstrated in patients with HCV (whether diabetic or not), and particularly in those infected by HCV genotype 3 [72].

Data from different sources appear to indicate that steatosis precedes the development of liver fibrosis. Indeed, by promoting greater hepatic periportal necrosis, steatosis may even accelerate the progression of fibrosis [82,100]. The underlying mechanisms may be similar to those governing obesity, where visceral lipolysis resistant to insulin suppression leads to excess in FFA in the liver due to the hyperinsulinaemic state. However, it is difficult to establish a strong correlation between steatosis and fibrosis. It has been suggested that the inflammatory state associated with steatosis might explain the link; however, this is not supported by evidence showing fibrosis progression between successive liver biopsies in HCV-infected patients with steatosis and minimal inflammatory hepatic lesions [100].
serum glucose levels in HCV-infected patients have been shown to have a greater profibrogenic impact during intermediate and late fibrosis than in its earlier stages. Thus, hyperglycaemia may play a role in the progression of fibrogenesis rather than in the initiation of the fibrosis process [39].

13. HIV–HCV coinfection

Up to 30% or more of HIV-infected patients are coinfected with HCV [101,102]. In this setting, the presence of HIV can worsen the severity of HCV disease. In coinfected individuals, HIV infection is correlated with a higher HCV viral load, and more frequent and severe liver fibrosis [103,104], as well as with increased mortality as a consequence of end-stage liver disease and hepatocellular carcinoma [105]. On the other hand, HCV seems to have little influence on the natural history of HIV [101,106].

Coinfection with HIV and HCV may also induce additive or synergistic effects on glucose and lipid metabolism, and on the liver, of infected patients. The risk factors associated with hepatic steatosis were evaluated in patients who had available histological data from the RIBAVIC study, a randomized controlled trial of pegylated IFN-α-2b plus ribavirin versus IFN-α-2b plus ribavirin for the initial treatment of chronic hepatitis C in HIV coinfected patients [107]. The prevalence of steatosis was high in HIV–HCV coinfected patients, and correlated with the same risk factors as for HCV infection alone. Steatosis was not correlated with the characteristics
of HIV infection (such as AIDS status, CD4 cell count and HIV viral load); also, the RIBAVIC and other studies failed to demonstrate a correlation between steatosis and antiretroviral therapy [108,109]. However, fibrosis severity and progression rate have been correlated not only with HCV and host factors (for example, age at infection or alcohol consumption), but also with the level of HIV-induced immunosuppression [110].

14. Implications for the treatment of HIV and HCV

This review describes the changing focus regarding the treatment of metabolic disorders in chronic viral diseases. Until recently, the therapeutic focus was on lipid disorders, but our current understanding is that the principal underlying issue is insulin resistance and liver damage (Fig. 1). The chronic viral state itself and the host immune response give rise to glucose and lipid metabolic disorders that, in turn, are risk factors for liver damage. In the case of HIV or HCV infection, such metabolic disorders can also occur independently of antiviral therapy. The different interactions between HCV and HIV, on the one hand, and insulin resistance, type 2 diabetes, steatosis and fibrogenesis, on the other hand, should be taken into account when determining the treatment and long-term follow-up of infected patients.

The outcomes of chronic HCV or HIV infection, and the presence of concurrent hepatic disorders such as steatosis and fibrosis, are compromised by the metabolic syndrome. This syndrome and its related risk factors can also influence the choice, efficacy and safety of antiviral therapy: for example, metabolic steatosis negatively affected the response to treatment in patients infected with non genotype-3 HCV whereas viral steatosis was not an influential factor [111].

Obesity and insulin resistance associated with steatosis might explain this impaired response to treatment. In a study of Spanish patients infected with genotype-1 HCV, insulin resistance independently predicted the response to anti-HCV therapy [70]. The underlying mechanism may be excess intrahepatic expression of cytokine signalling suppressors, such as SOCS-3, in obese insulin-resistant patients [112].

The impact of the metabolic syndrome on both cardiovascular and hepatic risk factors must also be considered in patients with chronic viral diseases. Indeed, the hepatic metabolic impairment that accompanies chronic viral infection may significantly increase the disease burden over time, as it is the root of more severe and progressive fibrosis.

Large gaps remain in our understanding of the metabolic changes and interactions in chronic viral infections. The impact of eradicating HCV or suppressing HIV infection on the metabolic syndrome is as yet undetermined. Recent data from HCV-infected patients successfully treated with IFN with or without ribavirin indicate that HCV clearance improves insulin sensitivity and hepatic function [77]. Further data are awaited with great interest.

Conflicts of interest

L. Slama has been a consultant for Vertex Pharmaceuticals (Europe) Ltd, and J. Capeau has been a member of advisory boards/consultant for Vertex Pharmaceuticals. L. Serfaty is a clinical investigator for Vertex Pharmaceuticals, and C. Le Camus and S. Gharaikhani are both employees of Vertex Pharmaceuticals. G. Pialoux has no conflicts of interest to report in relation to this publication.

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