1. Introduction

The hepatitis C virus (HCV) is a major cause of chronic liver disease worldwide. Its spectrum of severity, however, varies widely, as does its rate of progression towards cirrhosis. This depends on several host-related cofactors, such as age, gender, alcohol consumption, overweight and co-infections. The objective of this review is to discuss two of these cofactors: steatosis and insulin resistance. Although both may occur independently of HCV, a direct role of HCV infection in their pathogenesis has been reported. Whereas the virus-induced steatosis does not seem to have major clinical consequences, the so-called ‘metabolic’ steatosis and underlying insulin resistance may not only modify the clinical and histological course of chronic hepatitis C, but may also influence the response to interferon alpha-based therapy.

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as a result of alcohol consumption, are now most often seen in association with the metabolic syndrome. The concomitance of increased fatty acid synthesis and the free fatty acid overflow to hepatocytes that accompanies the metabolic syndrome are the major pathogenic mechanisms leading to fatty liver in these patients [3]. Given the current pandemics of overweight, it is not surprising that steatosis is so frequent in chronic hepatitis C. In fact, the prevalence of steatosis in patients with chronic hepatitis C varies between 50% and 80%, depending on the prevalence of alcohol consumption, overweight, diabetes and other risk factors of fatty liver [2,4]. This prevalence is higher than in the general population. In comparison, 30-35% of potential liver donors in the United States have steatosis at liver biopsy [5]. When all major factors of fatty liver are excluded, the prevalence of steatosis in chronic hepatitis C is still about 40%, which is twofold higher compared with the average prevalence of steatosis in chronic hepatitis B [2,6]. This observation alone suggests that HCV may be directly affecting intrahepatic lipid metabolism, resulting in a fatty liver; indeed, in the pre-serology era, the presence of fatty liver was widely considered diagnostic of non-A, non-B hepatitis.

The association between HCV and fatty liver is, in part, genotype-specific. Among patients with chronic hepatitis C, those with genotype-3 infections have more frequent and more severe steatosis than those with non-genotype-3 infections [7-10], hinting at the presence of steatogenic sequences within the genome of genotype 3: in patients with genotype-3 infection, fatty liver can occur in the complete absence of obesity and insulin resistance [11,12]. In addition, the severity of steatosis in patients with genotype 3 correlates with the level of HCV replication, both in liver [8] and in serum [9]. Steatosis is reduced or disappears when patients are successfully treated with antivirals, particularly if infected with genotype 3, while those with non-3 genotypes may retain a fatty liver even when cured of the virus [13,14]. A relapse after the end of therapy may cause the reappearance of steatosis in patients in whom it had disappeared during therapy [15]. These observations suggest a viral etiology of fatty liver, at least in patients with genotype-3 infection. In non-genotype-3 infections, steatosis is most common in patients who are obese and insulin-resistant, and insulin resistance seems to be central in accounting for the pathogenesis of fatty liver in such cases [3,9,12].

The mechanism of triglyceride accumulation by HCV is multifactorial [16]. HCV can interfere with lipid metabolism at three levels: impaired lipoprotein secretion; increased lipogenesis; and impaired fatty acid degradation. Impaired secretion of lipoproteins from infected hepatocytes was the first mechanism proposed to explain HCV-induced steatosis. Serum levels of apolipoprotein B (apoB) and cholesterol are diminished in chronic hepatitis C [10,14,17], but return to normal after successful antiviral therapy, suggesting that HCV may interfere with very low-density lipoprotein (VLDL) assembly and/or secretion. The potential relevance of this viral effect on virion assembly and release is discussed below.

Experimental models have shown that the HCV core protein is sufficient to induce triglyceride accumulation in hepatocytes [18-20]. The accumulation seems to occur to a slight extent in most viral genotypes, but genotype 3a is the most efficient [20]. In the transgenic mouse, the HCV core protein inhibits microsomal triglyceride transfer protein (MTP) activity [19]. Since this enzyme plays a key, rate-limiting role in VLDL assembly, the consequence of its inhibition is the accumulation of triglycerides. Recent data in human liver are in agreement with this mechanism, since the MTP mRNA levels are reduced in the liver of chronic hepatitis C patients, especially those with steatosis [21].

As a second mechanism, HCV may induce steatosis via increased synthesis of fatty acids by upregulating the sterol response element binding protein 1c (SREBP-1c) [22,23]. Yang et al. [24] confirmed these data indirectly by providing evidence of a causal relationship between HCV infection and the level of fatty acid synthase (FAS). They hypothesized that upregulation of FAS results in increased lipogenesis. If so, HCV infection could directly increase lipogenesis, contributing to the formation of steatosis. The HCV core protein may also bind to and activate the DNA-binding domain of retinoid receptor α (RXRα), a transcription factor that controls, among other functions, lipid synthesis [25].

Finally, HCV may impair fatty acid oxidation. Transfection of hepatoma cells with the HCV core protein leads to reduced expression of peroxisome proliferator-activated receptor α (PPARα), a nuclear receptor regulating several genes involved in fatty acid degradation [26]. PPARα mRNA is significantly reduced in the liver of patients with chronic hepatitis C [27,28].

A phenylalanine residue at position 164 of the core encoding sequence—present in genotype 3a, but replaced by tyrosine in all other genotypes—seems to be associated with activation of fatty acid synthetase and accumulation of big lipid droplets in hepatocytes [29,30]. However, in a recent study by Piodi et al. [31], although cells transfected with genotype 3a contained larger lipid droplets than cells transfected with genotype-1b sequences, there were no genetic differences between genotype-3a core proteins in patients with and without HCV-induced steatosis. The authors suggested that other viral proteins—or even host factors—could modulate the development of hepatocellular steatosis in patients infected by HCV genotype 3a.

The recurring question is: If HCV induces steatosis, why does it do so? Is HCV benefiting from the accumulation of triglycerides? Is steatosis increasing viral fitness or its rate of replication? Clinical trials of the treatment of chronic hepato-
titis C patients with steatosis [13,14] have shown that HCV replication precedes steatosis—not the other way around—and, therefore, it is unlikely that steatosis per se is a necessary factor for the HCV life cycle to proceed. However, some comments are needed in view of the known activation of HCV replication—at least in vitro—by fatty acids, especially saturated and monounsaturated, and by the observation that, in the same in vitro model, inhibition of fatty acid synthesis blocked HCV replication [32]. HCV replicates in association with cell membranes [33]; fatty acids are likely to be required to maintain a proper membrane structure. The HCV core protein has a strong affinity for intracytoplasmic lipid droplets (LD) and accumulates on their surfaces [34], a process mediated by its middle domain [35]. The transfer of core protein from the endoplasmic reticulum, where it is synthesized, to the surface of LD requires proteolytic processing [36]. Once localized to the LD, the core protein recruits the HCV replication complex, an event that requires interaction with non-structural protein 5A (NS5A) [37]. It must be mentioned that LD are fat-storing organelles physiologically found in hepatocytes and that, therefore, they are preexisting HCV infection. HCV core binds to LD independently of viral genotype and the presence or absence of steatosis in the liver of patients from which the isolate has been derived [31]. Thus, co-localization of the HCV core with LD and accumulation of fatty acids within hepatocytes are two events that should be considered as independent of each other. While it is clear that HCV replication and virion assembly requires fatty acids and LD, there is no evidence that steatosis—the excess accumulation of fat in cytoplasm—is indeed increasing viral replication. On the contrary, coalescence of LD into big steatosis droplets would reduce the effective surface area needed by the virus to correctly assemble mature virions.

Other evidence points towards the hypothesis that virus-induced steatosis is unfavorable to HCV. We noted that HCV decreases MTP activity, which results in the blockade of VLDL assembly and steatosis formation [19,21]. On the other hand, it has been shown that HCV virions are secreted via the intact VLDL pathway [38], and that MTP activity is necessary for HCV to be secreted, since silencing apoB or inhibiting MTP activity with the grapefruit flavonoid naringenin would block HCV secretion by about 80% [39]. Thus, HCV, while inducing steatosis, seems to block a pathway that is necessary for its mature virion secretion: for this reason, virus-induced steatosis is as favorable to HCV as would be its attempted suicide. We can only deduce that proper secretion of genotype 3 virions relies on any residual activity of MTP and that steatosis is, in fact, reducing virion secretion. Whether this results in a benefit for the virus in terms of reduced viral spread, replication and viral protein expression, a device frequently used by viruses to favor its persistence of infection, remains purely speculative at present. In conclusion, the significance (if any) of the occurrence of steatosis in some patients infected with HCV, especially genotype 3, remains unclear.

3. Clinical impact of HCV-induced steatosis

Steatosis has been reported to contribute to disease progression in chronic hepatitis C [2,3,9]. Steatosis on the initial biopsy has been associated with a more rapid development of fibrosis [40-45], higher risk of hepatocellular carcinoma (HCC) [46] and decreased response to antiviral therapy [43]. In view of the discordant data reported in the literature, especially concerning the relative contribution of the different genotypes to liver fibrosis [41-45], we carried out a vast meta-analysis on individual patients’ data (the HCV MAID Study), collecting information on 3,068 patients from 10 centers around the world [47]. The results of this analysis suggest that the relationship between steatosis and fibrosis holds true essentially for patients with non-genotype-3 infections, notably those with genotype 1. In other words, the steatosis observed in patients with genotype-3 infection, despite its frequent occurrence and severity, does not appear to lead to an accelerated course towards cirrhosis [47]. Previous reports suggesting otherwise may have artefactually emphasized a spurious association between HCV-induced steatosis and fibrosis due to center-specific features of the study population such as overrepresentation of cirrhosis patients [44].

The association between steatosis and response to interferon alpha-based therapy is similarly true only for patients with non-virus-induced steatosis. An extensive study has confirmed this view [14] and, in another report [48], patients with genotype 3 and the most severe steatosis had very high rates of sustained virological response. Conversely, steatosis of other origin, essentially insulin resistance, is certainly associated with a poor response to therapy [14]: the mechanisms underlying this relationship are discussed below.

Finally, steatosis is often considered as a pathological condition that worsens an insulin-resistant state. However, in the case of HCV-induced steatosis, this does not seem to be true. In fact, not only do patients with HCV genotype 3 seem to have the lowest levels of insulin resistance [49], but they are also comparable to patients with and without steatosis [45]. Experimental models have also elegantly shown how hepatocellular steatosis and insulin resistance are not necessarily linked to each other [50].

In conclusion, steatosis can be induced directly by HCV, especially in genotype-3 infected patients. In some, fatty liver, mostly macrovesicular, can be severe, and as much as 80-90% of hepatocytes may contain big lipid droplets. Despite this, the clinical impact seems overstated, and virus-induced fatty liver does not accelerate liver disease progression, reduce the rate
of response to interferon alpha or worsen insulin resistance. Further studies may clarify the significance of viral steatosis in the HCV life cycle and its interaction with the host.

As far as the clinical management of virus-induced fatty liver is concerned, no therapeutic measures are indicated in addition to the standard management of chronic hepatitis C. Extensive diagnostic workups aimed at the identification of rare forms of fatty liver should be limited to special cases where the pathogenesis of steatosis is unclear. In most patients, severe steatosis, with genotype-3 infection, accompanied by high levels of HCV RNA and, if available, low levels of apoB in serum [17], do not warrant additional diagnostic procedures.

4. HCV and insulin resistance

Insulin resistance is defined as a condition in which higher-than-normal insulin concentrations are needed to achieve normal metabolic responses or, alternatively, normal insulin concentrations are unable to achieve normal metabolic responses [51]. Even before we started measuring the level of insulin resistance in chronic hepatitis C patients, most often by measuring the homeostasis assessment score of insulin resistance, known as HOMA score, several reports suggested an association between HCV infection and diabetes.

Diabetes is a common complication of all liver diseases, independent of the etiology, and especially in the advanced stages. However, clinical and experimental data suggest a direct role of HCV in the perturbation of glucose metabolism. Historically, the first observation that cirrhotic patients infected with HCV may have type 2 diabetes more frequently than do patients with cirrhosis of other origin was published by Allison et al. in 1994 [52]. A subsequent retrospective analysis of 1,117 patients with chronic viral hepatitis [53] reported type 2 diabetes among 21% of HCV-infected patients, but only in 12% of HBV-infected persons. Multivariable analyses showed that HCV infection and age were independent factors predicting diabetes. In a further case-control study conducted by the same authors in a cohort of 594 diabetics and 377 patients evaluated for thyroid disorders, 4.2% of diabetic patients were infected with HCV, compared with only 1.6% of controls [53]. Another study conducted within the Third National Health and Nutrition Examination Survey (NANHES-III) suggested a significant association between HCV infection and diabetes among persons 40 years of age or older, with a risk increased by a factor of about 3 [54]. This raised the suspicion that diabetes may be due to the stage of advancement of liver disease rather than the viral infection. However, when the insulin-resistance score, a more sensitive and earlier marker of glucose metabolism derangement, was measured in a population of 121 chronic hepatitis C patients with portal or no fibrosis—in other words, at the early stages of disease—this was higher compared with the average HOMA score found among 137 healthy volunteers matched by gender, body mass index (BMI) and waist-to-hip ratio [49]. This work suggested that HCV may disturb glucose metabolism at a very early stage and, thus, independently of the degree of fibrosis.

All of the above studies failed to completely rule out the possibility that the higher prevalence among HCV-infected persons may partly depend on the higher risk of exposure to HCV through invasive medical procedures undergone by diabetic patients. If this were true, then HCV could merely be considered an iatrogenic infection of patients with diabetes repeatedly exposed to blood-contaminated tools, hence following the diagnosis of diabetes. To dispel this potential bias, compelling evidence comes from longitudinal studies. In a community-based cohort of 1,084 persons, aged between 44 and 65, enrolled in the Atherosclerosis Risk in Communities (ARIC) study and free of diabetes at baseline, 548 developed diabetes during a follow-up of 9 years [55]. After categorization of participants as low-risk or high-risk for diabetes, based on their age and BMI, and considering only those at high risk of diabetes, persons with HCV infection at the start were more than 11 times as likely as those without HCV infection to develop diabetes during follow-up. Among those at low risk, no increased incidence of diabetes was detected among HCV-infected persons. The authors concluded that a preexisting HCV infection could increase the risk of type 2 diabetes in those with recognized diabetes risk factors. A similar synergistic effect of HCV with other risk factors was observed in a more recent study from Taiwan. Wang et al. [56] analyzed a community characterized by a high prevalence of HBV and HCV infections to assess the temporal relation between these infections and the occurrence of diabetes. This study demonstrated that HCV infection—including HBV/HCV co-infection, but not HBV infection—could increase the risk of incident diabetes. The risk of diabetes for HCV-infected persons increased among younger persons. Again, a synergistic effect on the risk of diabetes was found in overweight and obese patients infected with HCV. The authors went as far as to recommend regular diabetes screening among anti-HCV-positive people, starting at a young age, especially for those at high risk. Finally, additional epidemiological evidence comes from longitudinal studies carried out in transplant patients. In the liver-transplant setting, HCV infection is a risk factor for development of type 2 diabetes after transplantation [57-60], and a recent meta-analysis has shown that anti-HCV-positive renal-transplant recipients are also characterized by a marked increase of the risk of post-transplant diabetes [61]. This risk is clinically meaningful because the excess risk of death in HCV-positive renal-transplant recipients may be at least partially attributed to post-transplant diabetes and its complications [61].
Arsenally glucose metabolism disturbances among HCV-infected population clearly depends not only on the sensitivity of the diagnostic tool, but also on the baseline epidemiology of the population under study. Recent reports show how conflicting the data may be. In Sweden, the prevalence of HCV is lower than elsewhere—estimated to be around 0.33% [62]. Sjöberg et al. [63] determined the HCV prevalence in a large cohort of patients with diabetes to assess if such an association could be found in a region with a low prevalence of HCV. In this cohort of diabetic patients (including both type 1 and type 2), the prevalence of HCV was comparable to that found in Swedish healthcare workers (0.68%). They concluded that, in a region with low HCV prevalence, hepatitis C has no etiological role in the development of diabetes, suggesting the involvement of other pathophysiological mechanisms. Another recent study from Japan, based on a different design, came to a similar conclusion. Imazeki et al. [64], in a cross-sectional study, investigated the prevalence of diabetes and insulin resistance in patients with chronic hepatitis C, and compared it with that in patients infected with HBV and those who cleared HCV after interferon treatment as controls. They found the prevalence of insulin resistance to be higher in patients infected with HCV than in those whose HCV had been cleared, but multivariable logistic-regression analysis did not identify HCV infection as an independent risk factor for insulin resistance after adjusting for age, BMI and transaminase levels. There were no differences in the prevalence of diabetes or insulin resistance between patients with genotypes 1 and 2 (genotype 3 is uncommon in Japan). They concluded that, in Japan, factors other than HCV, such as older age, male gender, increased BMI and presence of cirrhosis, might be important risk factors for the development of glucose abnormalities in chronic hepatitis C.

In an attempt to definitively clarify this issue, an important meta-analysis was performed and recently published [65], the first such study to specifically address the association between HCV infection and risk of diabetes in the general population. The significant excess risk observed in the meta-analysis of prospective studies (adjusted hazard ratio = 1.67) was highly consistent with the significant excess risk observed in the meta-analysis of retrospective studies (adjusted odds ratio = 1.70), adding further support to the retrospective data. Similarly, the overall unadjusted pooled estimator demonstrated a significant twofold excess risk. Taken together, the findings of this meta-analysis clearly indicate that chronic hepatitis C is associated with a modest, but significant, increase in the risk of developing type 2 diabetes in comparison to uninfected controls [65].

Data suggesting a relationship between the severity of insulin resistance and HCV replicative levels are inconclusive. Recent work seems to suggest that this is the case [66,67], but it is still not clear whether HCV replication in these patients directly increases insulin resistance or whether hyperinsulinenia stimulates viral replication, as suggested by previous in vitro data [68]. The poor correlation may be due to the fact that the overall score of insulin resistance largely depends on contributions from adipose tissue and muscle, extrahepatic compartments not affected by HCV.

If HCV is increasing the level of insulin resistance or predisposes to the development of type 2 diabetes in high-risk individuals, then curing hepatitis C should result in an improvement in HOMA score and a lower incidence of glucose metabolism dysfunction in the post-treatment follow-up. Romero-Gómez et al. [69] assessed the effects of sustained virological response, together with host and viral factors, on the incidence of impaired fasting glucose and/or type 2 diabetes in 1,059 patients with chronic hepatitis C treated with a combination of pegylated interferon alpha plus ribavirin. Their results showed that the eradication of HCV reduced by half the incidence of type 2 diabetes and/or impaired fasting glucose in the course of post-treatment follow-up. Abnormal glucose values were detected more often in chronic hepatitis C, in older patients, those with steatosis and those who were overweight. Similarly, Kawaguchi et al. [70], in their study on 89 patients who underwent repeated liver biopsy before and after therapy, demonstrated that clearance of HCV improved the HOMA score and the intrahepatic expression of insulin receptor substrates (IRS) 1 and 2, two hepatocellular transducers of the insulin signal.

Both studies seemed to indicate that HCV itself is involved in the development of insulin resistance. Conversely, in another study, Giordanino et al. [71] evaluated and followed-up 202 patients with chronic hepatitis C treated with antiviral therapy. They concluded that the cumulative incidence of both impaired glucose tolerance and diabetes in chronic hepatitis C patients who maintain a long-term clearance of the virus is better predicted by baseline-recognized risk factors of diabetes than by HCV eradication. In fact, there was no significant difference between non-responders and long-term responders regarding the incidence of diabetes. The baseline features predicting diabetes, such as older age, BMI and family history of diabetes, maintain their critical role even in sustained virological responders. It is possible that HCV eradication is beneficial in the short term and that, as follow-up proceeds, major risk factors of diabetes take over.

5. HCV interference with insulin signaling

Experimental data suggest a direct interference of HCV with the insulin cascade. This was first shown by a study where liver specimens obtained from 42 non-obese and non-diabetic HCV-infected subjects and 10 non-HCV-infected subjects matched for age and BMI were exposed ex vivo to insulin, and examined for the contents and phosphorylation/activation status of insulin-signaling molecules [72]. Insulin-stimu-
lated IRS-1 tyrosine phosphorylation was decreased twofold in HCV-infected patients compared with non-HCV-infected subjects, and this was accompanied by significant reductions in IRS-1/p85 phosphatidylinositol-3-kinase association, IRS-1-associated PI3-kinase enzymatic activity and insulin-stimulated Akt phosphorylation [72]. Thus, in patients with chronic hepatitis C, direct interactions between viral products and insulin-signaling components occur that may contribute to insulin resistance, thereby leading to the development of type 2 diabetes in high-risk individuals, as already stated above. However, the nature of such molecular interaction(s) is still under debate. In the transgenic mouse model [73], the core-encoding region of HCV is sufficient to induce insulin resistance. This effect is annulled by treatment with anti-TNF-α antibodies, suggesting an increased level of serine phosphorylation of IRS-1 induced by TNF-α. The effect of the HCV core protein has been also tested in vitro, where an increased proteasomal degradation of IRS-1 and -2 via activation of the suppressor of cytokine signaling (SOCS)-3 was observed [74]. However, in vitro data are diverse, and the mechanisms may be variable, depending on the system and/or the viral genotype tested. Increased endoplasmic reticulum (ER) stress has been reported that may render the cell insulin-resistant [23]. Work from Pazienza et al. [75] showed downregulation of peroxisome proliferator-activated receptor γ (PPARγ) and upregulation of SOCS-7 in cells transfected with the core protein of genotype 3, whereas the core protein of genotype 1b activated the mammalian target of rapamycin (mTOR), findings that were confirmed using agonists for PPARγ (rosiglitazone) or short interfering RNA for SOCS-7 [76]. Another study has identified the overexpression of P2A in cells expressing HCV and in the liver of chronic hepatitis C patients as a factor contributing to the pathogenesis of insulin resistance associated with HCV [77]. Recently, the role of the HCV-induced activation of the c-Jun N-terminal kinase (JNK) has been emphasized: the HCV core protein-mediated Ser(312) phosphorylation of IRS-1 was inhibited by a JNK inhibitor in an in vitro infection assay using cell-culture-grown HCV genotypes 1 and 2 [78].

The role of oxidative stress is suggested by results obtained in chronic hepatitis C patients. Mitsuyoshi et al. [78] evaluated 203 histologically confirmed chronic hepatitis C patients with HCV genotype 1 or 2 infection. HOMA and serum levels of thioredoxin (Trx), a marker of oxidative stress, were found to be significantly correlated with each other, even after adjustment for BMI. Further studies are, however, necessary to clarify the role of oxidative stress in the pathogenesis of insulin resistance in the liver of chronic hepatitis C patients. An additional indirect viral effect, mediated by increased levels of TNF-α as suggested by the transgenic mouse model, has been corroborated by some human studies in which an exaggerated intrahepatic TNF-α response, resulting in insulin resistance and a higher risk of developing diabetes, has been reported [79,80].

6. Clinical consequences of insulin resistance in hepatitis C

There are two major clinical consequences of the insulin-resistant state associated with hepatitis C, independent of its pathogenesis: the accelerated progression of liver fibrosis; and the reduced response to therapy. We have already mentioned the role of non-virus-induced steatosis as an independent predictor of fibrosis [47]. The mechanisms by which non-viral steatosis can promote liver fibrosis range from oxidative stress to proinflammatory cytokines, insulin resistance and increased susceptibility to apoptosis.

The association between HCV and oxidative stress has been reported in transgenic mice [81,82]. In the presence of steatosis, oxidative stress is increased in HCV infection and may promote fibrogenesis, similar to the so-called ‘second strike’ proposed in the pathogenesis of non-alcoholic steatohepatitis. Proinflammatory cytokines may also mediate fibrogenesis in patients with steatosis, although it is unclear how steatosis can promote and/or amplify this process. Our multicenter meta-analysis [48] using individual data from 3,068 patients with chronic hepatitis C showed that steatosis is associated with both increased liver inflammatory activity and fibrosis.

Insulin resistance is associated with liver fibrosis and, when the multivariable model includes both steatosis and insulin resistance, only the latter is found to be an independent predictor of fibrosis stage [49]. These observations have been largely confirmed [83-85], although the molecular mechanisms leading from the insulin-resistant state to accelerated fibrogenesis are unclear. In non-alcoholic steatohepatitis, hyperglycemia/hyperinsulinemia may be directly stimulating hepatic stellate cells to produce connective tissue growth factor leading, in turn, to increased collagen fiber deposition [86]. Interestingly, weight reduction and increased physical activity in patients with chronic hepatitis C and steatosis were sufficient, in the short term, to reduce both liver fibrosis score and hepatic stellate cell activation [87], although these data await independent confirmation. Finally, increased liver cell apoptosis has been reported to correlate with steatosis [88], as reflected by the elevated caspase activity in serum [89]. In the presence of steatosis, increased apoptosis was associated with activation of stellate cells and a higher stage of fibrosis, which is in agreement with the hypothesis that a steatotic liver is more vulnerable to liver injury and suggesting another mechanism of accelerated liver disease progression in the presence of steatosis [88].

Steatosis decreases the response to interferon alpha-based therapy in chronic hepatitis C [14,90,91]. As in the case of accelerated fibrogenesis, this association seems to be limited
to patients with metabolic steatosis, suggesting that the mechanism of reduced response to treatment may be again mediated by insulin resistance. This was confirmed by studies in patients with genotype 1 [92] or genotypes 2 and 3 [93], where the sustained virological response rate was inversely correlated with the HOMA score before therapy. Indirect evidence in favor of this negative association comes also from the reduced response to treatment reported among African Americans, very likely due to a high rate of visceral obesity and insulin resistance [94], and the correlation between high levels of circulating TNF-α, typically observed in insulin resistance, and reduced response to interferon alpha therapy [95]. The molecular link between insulin resistance and resistance to interferon alpha seems to be represented by the increased levels of SOCS-3 in liver [96]. SOCS-3 is not only promoting the proteasomal degradation of IRS-1, leading to impaired insulin signaling [74] but is also, together with other members of the SOCS family, a negative regulator in the transduction of the interferon alpha signaling [97]. Thus, HCV may activate some members of the SOCS family as a mechanism to inhibit interferon alpha signaling while simultaneously impairing insulin signaling. Whether this mechanism can be exploited pharmacologically, with drugs aimed at reducing insulin resistance while improving the responsiveness to interferon alpha, remains to be fully explored. Although preliminary data from a pilot study [98] have been disappointing, further schedules should be evaluated. For the time being, the only clinical-management measure that can be reasonably proposed for patients with chronic hepatitis C and an insulin-resistant state associated with the metabolic syndrome involves the lifestyle changes that are commonly recommended for all patients with an increased cardiovascular risk. Given the impact that diabetes has not only on liver fibrosis progression, but also on the development of hepatocellular carcinoma [99], more targeted and effective drugs are eagerly awaited.

Conflicts of interest: The authors have none to declare.

References


