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**Are metabolic factors still important in the era of direct antiviral agent’s in patients with chronic hepatitis C?**

Grasso A *et al.*Metabolic factors and direct antiviral agents

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**Abstract**

The high rate of sustained viral response (SVR) to boceprevir or telaprevir-based triple therapy in hepatitis C (HCV)-related, non-cirrhotic naïve patients or relapsers to previous antiviral treatment leads clinicians to believethat the impact of metabolic host factors on SVR is minimal when triple therapy is used, unlike what is observed with the peginterferon and ribavirin schedules. This concept is strongly expressed by some opinion leaders on the basis of the data derived from sub-analyses of registrative trials as well as from a post-hoc analysis of the phase II C208 clinical trial. The perception of unrestrainable therapeutic success with the use of newer, more powerful antivirals is now reinforcedby the brilliant results obtained with sofosbuvir, an HCV NS5B polymerase inhibitor**,** as well as by the data from the phase II and III studies on the various combinations of second-generation NS3/4A inhibitors, NS5A and/or NS5B inhibitors. However, agreat deal of concern has emerged from the real world scenario in which patients are often older and have more comorbidities than patients in the “world of trials”. Furthermore, many of them have advanced fibrosis and previous failurewith peginterferon and ribavirin treatment. Some data from the recent literature suggest that the host metabolic factors may play a minor but non-negligible role in these difficult-to-treat patients, an issue that will hopefully be investigatedin further studies. This Editorial aims to provide a detailed analysis of the role that host metabolic factors played in the past and what rolethey may play in the era of direct antiviral agents.

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**Key words:** Metabolic factors; Insulin resistance; Direct antiviral agents; Chronic hepatitis C

**Core tip:** This editorial explores the past and present role of metabolic factors by analyzing the data that hasemerged from the post hoc analysis of registrative trials of direct antiviral-based treatment. Low-density lipoprotein-cholesterol and statin use proved to be predictors of sustained viral response (SVR) in both boceprevir and telaprevir-treated patients, respectively. Furthermore, HOMA-IR negatively influenced SVR in prior partial and null responders treated with telaprevir-based schedules. By transferring these data to the real world scenario in which patients have comorbidities, advanced fibrosis and prior failure to antiviral treatment, we believe thatmetabolic factors might play a non-negligible role in influencing antiviral response, even in triple therapy.

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**INTRODUCTION**

More than 170 million people are chronically infected with thehepatitis C virus (HCV) worldwide[1], thus HCV has become the main cause of chronic liver disease leading to death from liver failure or hepatocellular carcinoma (HCC) in many Western countries and in Japan[2]. Viral eradication resulting from antiviral treatment has led to a decrease in these complications. However, treatment with pegylated interferon and ribavirin, which has been the standard-of-care therapy for chronic hepatitis C for the last decade, has been able to cure only about 40%-50% of patients with hepatitis C genotype-1, the main strain in Europe and the United States[3-6].

Genotype 1 is the main viral-related variable associated with treatment failure[3,4]. However, a number of other pretreatment variables related to the virus (high viral load) and to the host (interleukin 28b polymorphism, age, overweight, metabolic factors), as well as on-treatment variables (4-wk negativization of viral load) have been shown to affect the response to anti-viral dual therapy[7-10].

**HCV INFECTION AND METABOLIC SEQUELAE: WHAT WE LEARNED FROM THE PAST**

***Insulin resistance***

Epidemiological data suggest that HCV interfereswith the glucose and lipid metabolism. Patients with diabetes show a greater prevalence of HCV as compared to the non-diabetic population[11]. Moreover, the prevalence of diabetes is significantly higher in chronic hepatitis C patients than in those with chronic liver disease other than HCV[12]. Furthermore, it is wellknown that HCV infection is an independent risk factor for developingdiabetes[13]. These data suggest that HCV, rather than liver disease *per se*, predisposes patients to diabetes.The link betweenHCV and diabetes is the development of insulin resistance (IR), a metabolic prerogative of HCV (*i.e.*, IR is more than six fold higher in HCV patients than in those with HBV) [14]. IR, hepatic steatosis and body mass index (BMI) are related in a genotype-dependent fashion. In fact, HCV genotype 3 exerts a direct cytopathic and steatogenic effect on hepatocytes**,** thus resulting in a higher prevalence of steatosis and a lower prevalence of IR compared with HCV genotype 1, which very quickly inducesIR and some steatosis [15-17]. IR occurs very earlyin transgenic mice expressing the HCV core protein and may even precede the occurrence of hepatic steatosis, thus indicating that IR is not a consequence of hepatic steatosis [18], similarly to what is observed in humans [17]. Furthermore, IR is a profibrogenetic stimulus [17], thus patients with high IR show more advanced liver fibrosis than patients with low IR [19]. Finally, the association between IR and high HCV RNA levels [14] suggests a complex interplay between viral replication and insulin action. HCV may induce over-expression of the suppressor ofthecytokine signaling-3 (SOCS3) gene in liver tissue. This gene isinvolved in the interferon signaling pathway andis associated with poorer treatment outcome [20,21]. HCV core-induced SOCS3 may promote proteosomal degradation of the insulin receptor substrates1 and 2 (IRS1/2), thus inducing severe hepatic IR [22,23]. BothSOCS3 over-expression and hepatic steatosis promote intra-hepatic and systemic lipid oxidation, thusleading to an imbalance of total glucose disposal in the muscles and resulting in peripheral (and not only hepatic) IR [24].

**D**irect involvement of HCV in glucose metabolism has also been demonstrated “*in vivo*”. In fact, there is robust evidence showingthat IR improved significantly inpatients with HCV genotype 1 who achieved SVR compared with patients who did not obtain viral clearance after treatment [25,26]. Furthermore, achieving viral clearance is demonstrated to significantly reduce the risk of both type 2 diabetes in retrospective cohorts [27] and of *de novo* IR in non-diabetic HCV patients [28].

***Lipids***

Hepatic steatosis is also related, in a genotype-specific manner [29], to a decrease in serum levels of total cholesterol, low-density lipoprotein cholesterol(LDL-C) and apolipoprotein B (apoB), thus demonstrating the close link between HCV and lipids. A variable fraction of HCV in theserum circulates in lipoviroparticles (LVP), with very-low-density-lipoprotein (VLDL) containing apoB and apoE.LVP reach the highest levels in the post prandial phase, suggesting that their formation is a dynamic process [30]. Very recently, a strong correlation between the maximum amount of LVP *in vivo* and both IR and metabolic syndrome was reported, suggesting that lipids may play a role in HCV-induced IR [31]. ApoE is considered the centralcomponent of the HCV–host lipid interaction, mediating HCV infectivity*via* lipoprotein receptors [32]. Lipoproteins (LP) are easily endocytosed, thussupporting the hypothesis that HCV can use this association with LP to adhere tothe cell and subsequently enter the host cell by endocytosis [33]. Various cell surface receptors, including tetraspanin CD814, scavenger receptor class B member I, tight-junction proteins claudin-1 and occludin, and clathrin-mediated endocytosis have been proposed as entry factorsfor HCV, but the role each of them playsremains controversial. Recently, the Niemann- Pick type C1-like 1 gene (NPC1L1) receptor hascome to the attention of researchersin the view of a potentially new therapeutic antiviral strategy since it is the possible target of the receptor-blocker drug ezetimibe [34,35].

Few and inconsistent data have been reported on serum lipid level modifications during interferon therapy. Increased total cholesterol and triglyceride levels have been observed with interferon treatment, with a subsequent drop to pretreatment levels of both after discontinuing therapy, but with different trends depending on the HCV genotype [36,37]. In a small population of patients with genotype 2 and 3, viral clearance induced serum level modifications of lanosterol, a cholesterol precursor, suggesting a direct viral interference with the enzymes of sterol synthesis[29].

***The effects of IR on antiviral response to dual treatment***

Patients with high IR showa slower decay of HCV viral load than patients with low IR, even in the very early phase of treatment (first 24 h), suggesting that hyperinsulinemia reduces the cellular response to pegylated-interferon [38]. Furthermore, high IR has been associated with a low rate of rapid viral response (RVR) in genotypes 1 [39], 3 [40] and 4 [41].

Whether or not IR influences SVR rate has been a question of debatesince 2005 [9]. Two meta-analyses assessing the impact of IR on treatment outcome, both of which included fourteen studies with more than 2700 patients,were published in 2011 [42,43]. However, among the studies which failed to find an association between IR and SVR, the main baseline HOMA value, an indirect measurement of IR [44,45], was < 3 and the prevalence of advanced fibrosis or cirrhosis was also low or even absent [42]. This observation supports the hypothesisthat the HOMA value is predictive of response to antiviral treatment mainly in patients with advanced disease stage**.** Liver fibrosis is an event which may occur as a consequence of HCV-related chronic necroinflammatory activity or via HCV related IR, or probably both. However, non-HCV related IR (genetic, or related to true metabolic syndrome) may also occur since almost 25% of the general population has the metabolic syndrome stigmata [46]. On the basis of these data, we can assume that a proportion of patients with prevalent virus-related IR (likely those with lower fibrosis as well as a lower incidence of cardio-metabolic comorbidities) have lower HOMA values and a higher likelihoodof SVR after antiviral treatment, whereas other HCV patients with prevalent metabolic IR (likely those with the phenotype of metabolic syndrome) haveahigher probability of advanced fibrosis as well as higher HOMA levels and a lowerprobability of achieving SVR [28,42,47].

***The effects of obesity and lipids on antiviral response to dual treatment***

Obesity is another important metabolic cofactor that can affect antiviral response. It may induce IR and hepatic steatosis, both of which areassociated with poor antiviral response either directly or by ultimately promoting liver fibrosis. However, it has been demonstrated that obesity is an independent negative predictor of response to antiviral treatment regardless of genotype and cirrhosis [7].

Obesity is now considered an inflammatory condition, resulting in abnormal immune response to therapy. Adipose tissue secretes many proteins, including adipokines, which regulate hepatic and peripheral glucose and lipid metabolism. One of the adipokines secreted by adipose cells is leptin, whose expression is regulated by interleukin-1 (IL-1), tumor necrosis factor-á (TNF-á) and insulin. Although leptin secretion from adipocytes provides antiobesity signals, obese patients have elevated levels of leptin. This suggests an intrinsic leptin resistance in the obese, a complex phenomenon involving increased levels of SOCS3, which impairs post-receptor signaling and leads to reduced adenosine monophosphate–activated protein kinase (AMPK) activation [48,49].

Increased SOCS3 expression, which is associated with non response to antiviral treatment [20], has been demonstrated to beindependently associated with obesity in patients with chronic HCV viral genotype 1 [50].

Regarding the role of circulating lipid levels on theefficacy of antiviral treatment, there are few, but concordant data. Higher pretreatment total cholesterol and LDL-C [51,52], as well as lower triglyceride levels are independent variables associated with higher SVR rates [53].

***The interplay of Interleukin 28b polymorphisms and metabolic variables***

The relationship between IL28b polymorphisms and metabolic variables has been reported in several studies, thus emerging as a new and challenging issue. There is a close association between IL28b and lipid levels. In HCV genotype 1 patients, low apoE levels and higher LDL-C were associated with IL28b rs12979860 CC rather than CT/TT [54,55]. Both IL28CC and LDL-C were good predictors of SVR, but the predictive power of IL28CC is higher. Thus,the LDL-C level was foundto be a significant predictor of SVR, mainly for IL28 heterozygous CT patients [56].

Furthermore, lower steatosis [57] as well as lower IR [58] have been seen in genotype 1 patients with IL28b rs12979860 CC. In a recent, large cohort of genotype 1 patients from Italy, IL28b rs12979860 CC was associated with higher levels of total and LDL-C, lower levels of triglycerides, lower prevalence of IR and moderate-severe steatosis. However, only IR and steatosis were associated with IL28b rs12979860 CC after correcting for BMI and lipid profile, suggesting an indirect role of LDL-C status on IL28b polymorphism [58]. IR was found to have a predictivepower for SVR which is independent of IL28 genotype [59], although the likelihood of achieving SVR progressively increases from the lowest probabilityin patients carrying both negative predictors (IR and rs12979860 TT/TC; SVR = 20.7%) to the highestprobability in patients with no IR and rs12979860 CC (SVR=78.4%) [58]. These data give rise once again to the thorny question concerning the intimate pathogenetic interplay between metabolic and genetic host factors.

***Can pretreatment correction of the******metabolic co-factor improve SVR to dual treatment?***

One of the most intriguing and challenging tasks was to transfer the information regarding the predictive power of a metabolic variable for SVR to a practical ground. This gave rise to a series of studies aimed at improving SVR by correcting the metabolic factors before or during antiviral treatment.

Some studies with very small cohorts have explored the effectof a lifestyle intervention in obese and insulin-resistant subjects with chronic hepatitis C. BMI, HOMA values and leptin levels, but not TNF-á and IL-6, decreased significantly after aerobic exercise [60]. A more structured intervention based on a 24-wk dietary and physical activity regimens significantly reduced BMI and HOMA values [61] and could be an interesting baseline strategy in difficult-to-treat chronic hepatitis C patients who are obese and insulin-resistant prior tostarting peginterferon and ribavirin. However, to date**,** no studies have demonstrated the efficacy of this strategy. Tarantino et al. demonstrated that a low-calorie diet for 3 mo before starting antiviral therapy in patients with genotype 1-chronic hepatitis C resulted in a significant improvement in IR as well as a 60% “end-of-treatment” response rate in the low-calorie diet groupas compared to the control group (17.6%) [62].

More data have been reported on insulin sensitizing agents usedin combination with peginterferon and ribavirin. The randomized, double-blind TRIC-1 trial by Romero-Gomez *et al* analyzed 125 naive genotype 1 patients treated with peginterferon alpha-2a and ribavirin plus metformin or placebo on an intention-to-treat basis. Their final results showed that there was a significant decrease in both HOMA value and viral load during the first 12 wk, as well as an improvement in SVR rate in the metformin group as compared with the placebo group, but only in females [63]. While metformin failed to improve overall SVR, conflicting results have been obtained with other insulin sensitizing agents, mainly pioglitazone. Although comforting results have been obtained in genotype 4 [64], no improvement in SVR was observed byadding pioglitazone (30 mg per day) to peginterferon and ribavirin ascompared with the standard of care of dual therapy [65,66]. Similar negative results have been shown by Harrison *et al*[67] in a randomized controlled trial which compared pioglitazone plus standard of care *vs* standard of care alone. This study definitively demonstrated that even when pioglitazone was administered at an appropriate dose (45 mg per day), it failed to improve SVR, regardless of administration timing (*i.e.*, prior to starting the standard of care or during the peginterferon and ribavirin course) [67].

**ADVENT OF DIRECT ANTIVIRAL AGENTS AND THE NEW SCENARIO**

In recent years, several antiviral drugs that directly target HCV have been developed. These new drugs, known as direct-acting antiviral agents (DAAs), are designed to interfere directly with the HCV life cycle by inhibiting enzymes such as HCV NS3/4A protease and HCV NS5B polymerase, or other proteins such as NS5A. Two NS3/4A protease inhibitors, boceprevir and telaprevir, have become the first new drugs approved for the treatment of patients with genotype 1 HCV who have either not previously received treatment or who failed to achieveSVR with previous therapy [68]. These new drugs, however, must be given with peginterferon and ribavirin because of their low barrier to viral resistance when they are used as monotherapy, and this may limit efficacy. A further limitation is due to overall side effects resulting in higher discontinuation rates. However, when candidates for this treatment are carefully selected, the overall SVR rates can almost double in naïve and even triple in relapsers to previous double therapy [69-75]. Thus, triple therapy is the new standard treatment for HCV genotype 1 chronic liver disease.

One of the questions under debate is whether the predictors of treatment failurethat are observedwhen using dual therapy in HCV genotype 1 alsoexert a negative influence in triple therapy.

***What we know******about metabolic factors and triple therapy***

Among the variables whichhave shownpredictive power for SVR in dual therapy, some of them, suchas IL28b polymorphism, fibrosis and the 4-wk viral response in both naiveor previously treated patients, have also been highlightedin triple therapy on the basis of data emerging from registrative trials.Metabolic factors seem to play either no role at all, or only a minor one in influencing SVR in the context of triple treatment. However, some considerations have to be made when lookingcarefully at the post-hoc analysis of landmark phase-III trials**.**

In theboceprevir-based SPRINT-2 trial, two metabolic variables were associated with SVR, but only statin use proved to be an independent predictor of SVR (OR 3.4; 95%CI: 1.1–10.7; *P* = 0.04), whereas BMI was not retained in themultivariate model after adjustment for other variables [72].

In RESPOND-2, a boceprevir-based trial focusing on previously treated patients, both theresponse-guided treatment (RGT) group and the48-wk triple treatment group had a significantly higher SVRrate compared with dual treatment. However, in obese patients (BMI ≥ 30), a 10% lower SVR rate was observed in theRGT groupcompared with the48-wk triple treatment group (56% *vs* 65%) [73].

A sub-analysis of baseline predictors in the SPRINT-2 and RESPOND-2 trials showed that a BMI ≤ 30 was significantly associated with SVR and with a ≥ 1 log10 HCV-RNA decline at week 4 in untreated patients but not in patients previously treated with peginterferon and ribavirin [76].

In the two telaprevir-based studies carried out onuntreated patients, bothADVANCE [77] andILLUMINATE [75] showed a higher SVR rate in the RGT arms compared with thedouble treatment arm, regardless of diabetes and obesity. In the ADVANCE study, although a 30% greater improvement in the SVR rate of patients receiving telaprevir for 12 wk was achieved in all 3 BMI groups (< 25, 25-30 and > 30) as compared to the control group, a 12%-16% lower SVR rate was observed in overweight and obese patients compared to normal weight patients.

An important contribution was provided by Serfaty *et al* [78] in their post-hoc analysis of the phase II C208 clinical trial [79]. In this study, which is the firstto focus on the influence of baseline metabolic variables on SVR in patients treated with triple therapy, only LDL-C was associated with SVR (even in multivariate analysis), thus confirming its predictive role for SVR even in thetelaprevir-based triple regimen and not only in dual therapy. However, this is notthe case for baseline IR measured by theHOMA index, which did not show any relationship with SVR. Furthermore, the HOMA index did not influence the 4wk HCV RNA decline, nor werethe rates of HCV RNA undetectability at week 4 found to differ among patients with or without IR. However, this is not surprising since  baseline HOMA values werenot found to be associated with SVR in many European studies in which the studypopulation had a low prevalence of advanced fibrosis and a relatively low BMI [39,40,80,81]. This may suggest that a higher prevalence of “viral” IR, which can easily be counteracted by antivirals, actually does exist in this population of patients. The significant association between HCV RNA and HOMA values in the study of Serfaty *et al*, as well as the improvement of HOMA in patients who achieved SVR compared with those who did not, further confirm the direct “*in vivo*” involvement of HCV in IR pathways. On the other hand, a powerful**,** combined effect on suppressing HCV viremia and rapidly lowering IR was previously observed using a 14-d course of danoprevir monotherapy, *i.e.*, another powerful**,** selective inhibitor of NS3/4A HCV serine protease. Interestingly, overweight patients had a greater decrease in HOMA values than patients with normal BMI, despite a similar decrease in serum HCV RNA, suggesting a complex interplay between these two variables. The authors hypothesizean anti-inflammatory or insulin sensitizing effect of danoprevir [82].

Other important data concerning IR were obtainedfrom a post-hoc analysis of the REALIZE phase III study which was carried out to assess the impact of IR on virological response to a telaprevir-based regimen in previously treated patients. Baseline HOMA values were found to beassociated with SVR at univariate analysis (TVR: OR 0.76; 95%CI: 0.60-0.96) but not after adjustment for other baseline prognostic factors (TVR: OR 0.95; 95%CI: 0.71-1.29) [83]. SVR decreased as HOMA values increased,both in the control group and in thepooled T12-PR48 group where, however, this trend was observed only in prior partial and null responders, but not in prior relapsers.

In summary, on the basis of all these data we can say that LDL-C and statin use proved to be predictors of SVR in telaprevir and boceprevir-treated patients, respectively. Obesity may negatively influence rapid virologic decline as well as SVR in previously naÏve patients treated with a boceprevir-based regimen. To the best of our knowledge, no sub-analysis regarding the impact of obesity on SVR has **ever** been carried out for telaprevir. No data on HOMA are available for boceprevir. HOMA values were reported as being univariately associated with SVR in a telaprevir-based trial on previously treated patients. In naive patients treated with a telaprevir-based regimen, theHOMA value was not a predictor of SVR, nor was it found to be associated with rapid virological response.

However, some comments have to be made.First, we have no data on the real weight of baseline metabolic factors in patients with less favorable probability of response, such as those with advanced fibrosis and/or non-CC IL28b. It is reasonable to suppose that in patients with advanced fibrosis or cirrhosis, as well as in priorpartial or null responders to dual therapy and in whom non-CC IL28b is highly prevalent, metabolic IR, metabolic syndrome and obesity may be significant cofactors of non response to triple therapy. Hopefully, this will be an issuefor further studies. Secondly, in a real world setting we have to face a change in the epidemiology of candidates to triple therapy compared with the “world of trials”. In the “real world scenario” we have to expect a higher prevalence of patients over 65 years of age who haveoften previously beentreated with dual therapy and have a higher prevalence of comorbidities, including hypertension, dyslipidemia and diabetes. In this context, many patients might experience either a worsening in the sensitivity to interferon as well as a higher probability of side effects when a protease-inhibitor is added to therapy.

These points seem to have been taken into consideration by UK consensus guidelines for the use of protease inhibitors in the treatment of HCV genotype 1 infected patients.These guidelines recommend evaluating the presence of factors predictive of poor response to therapy, suchas BMI and type 2 diabetes among others [84].

Currently**,** an enormous effort is being made by researchers and companies to provide physicians with new and more powerful drugs with a high genetic barrier and able to work on several HCV genotypes. Recently, phase II and III studies on sofosbuvir,a new nucleotide analogue HCV NS5B polymerase inhibitor used in combination with peginterferon and ribavirin in genotypes 1, 4, 5 and 6 or in combination with ribavirin in genotypes 2 and 3, showed a highrate of SVR, up to 90% in untreated genotype 1 patients after a 12-wk regimen, with no additional side effects to those occurring with peginterferon and ribavirin [85-87].

New combinations of drugs with interferon-free schedules are under evaluation in phase II or III studies [88-91]. Hopefully, by the end of the decade the holy grail of a pangenotypic oral association of highly powerful drugs will be able to cure virtually all patients. In this scenario, the role ofpredictors of SVR will rapidly fade**,** but we have to keep in mind that in the short amount oftime that separates us from the availability of new and more powerful treatmentschedules, many patients will have to be treated with boceprevir and telaprevir-based triple therapy. Furthermore, many patients around the world have no, or only limited access to DAAs. With this in mind, SVR predictors remain important tools that are available to us in order to assign patients to the best treatment schedules.

**CONCLUSION**

Baseline metabolic factors seem to have a minor, though likely not negligible role in influencingantiviral response to direct antiviral agent-based treatment in patients with genotype 1 chronic hepatitis C. Further studies aimed at clarifying their role in a subpopulation of unfavorable candidates to this treatment, suchas patients with advanced fibrosis or prior partial or null responders to peginterferon and ribavirin, are needed.

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