Published in final edited form as:

Hepatology. 2009 October ; 50(4): 1030–1037. doi:10.1002/hep.23219.

Hepatitis C Virus Infection and Its Clearance Alter Circulating Lipids: Implications for Long Term Follow-up

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Abstract

Hepatitis C associated hypolipidemia has been demonstrated in studies from Europe and Africa. In 2 linked studies we evaluated the relationship between hepatitis C infection and treatment with lipid levels in an American cohort and determined the frequency of clinically significant post-treatment hyperlipidemia. A case-control analysis of patients with and without hepatitis C was performed. The Hepatitis C Group consisted of 179 infected patients. The Uninfected Control Group consisted of 180 age matched controls. Fasting cholesterol, low density lipoprotein (LDL), high density lipoprotein and triglycerides were compared. The second group was a retrospective cohort (Treated Hepatitis C Group) of 87 treated Hepatitis C patients with lipid data before and after therapy. In the case-control analysis, the Hepatitis C Group had significantly lower LDL and cholesterol than the Uninfected Control Group. In the retrospective cohort, patients in the Treated Hepatitis C Group who achieved viral clearance had increased LDL and cholesterol from baseline compared to patients without viral clearance. These results persisted when adjusted for age, sex and genotype. 13% of patients with viral clearance had increased LDL and 33% experienced increases in cholesterol to levels warranting lipid lowering therapy.

Conclusion—Hepatitis C is associated with decreased cholesterol and LDL levels. This hypolipidemia resolves with successful hepatitis C treatment but persists in non-responders. A significant portion of successfully treated patients experience LDL and cholesterol rebound to levels associated with increased coronary disease risk. Lipids should be carefully monitored in persons receiving antiviral therapy.

Keywords

Cholesterol; low density lipoprotein; hypolipidemia; anti-viral therapy; sustained virologic response

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Over four million Americans are infected with chronic hepatitis C. Current best therapy consists of pegylated interferon and ribavirin which results in sustained virologic response (SVR) in only half of patients.(1) Ongoing research into the HCV lifecycle has demonstrated a strong interaction between the virus and intracellular lipids, suggesting that host lipids play an important role in viral replication.

Several important lipid-HCV interactions have recently been elucidated. First, host serum lipids play a role in hepatitis C virion circulation and hepatocyte entry. A proportion of circulating hepatitis C viral particles are complexed with host triacylglycerol-rich lipoproteins, known as lipo-viroparticles.(2, 3) Lipo-viroparticles use LDL receptors on hepatocytes as points of entry and are associated with high rates of infectivity.(3–5) Once hepatitis C virions have entered hepatocytes their replication is again dependent on host lipid interactions. New hepatitis C virion formation requires viral binding to either a endoplasmic reticulum phospholipid membrane or to an endoplasmic reticulum-associated membranous web.(6) Additionally, HCV replication requires geranylgeranylation of the host protein FBL2, a process dependent on the host cholesterol synthesis pathway.(7, 8) Geranylgeranylation requires the production of geranylgeranyl, a non-sterol isoprenoid produced via the mevalonate cholesterol synthesis pathway. Inhibition of this pathway with HMG-CoA reductase inhibitors (HMGR inhibitors) leads to dissolution of the HCV replication complex *in vitro* while the addition of geranylgeraniol to HMGR inhibitor treated cells rescues HCV replication.(7) Finally, there is evidence that HCV secretion is linked to secretion of apolipoprotein B with silencing of apolipoprotein B RNA significantly inhibiting HCV secretion.(4, 9)

The importance of HCV-host lipid interactions has also been demonstrated clinically. Lower serum cholesterol levels have been noted in patients with chronic hepatitis C when compared to those with chronic hepatitis B.(10) A retrospective evaluation of a predominantly genotype 4 Egyptian cohort found that patients with chronic hepatitis C infection had significantly lower levels of LDL, cholesterol and triglycerides when compared to those who had never been infected with hepatitis C.(11)

We hypothesize that HCV, by interrupting cholesterol synthesis and using host lipids for replication, decreases circulating lipids and while clearance of the virus results in rebound of lipid levels. To explore these hypotheses, we evaluated the effect of hepatitis C infection on lipid homeostasis in U.S. subjects without and with chronic hepatitis C; we also evaluated the impact of viral clearance in subjects with chronic hepatitis C who received antiviral therapy. Additionally, and uniquely to our study, we sought to evaluate whether any post-HCV treatment lipid rebounds reached levels that are associated with increased risk of developing coronary heart disease and warrant treatment per the National Cholesterol Education Program Guidelines (NCEP)

Methods

This study was designed to answer several distinct questions and is composed of three unique groups evaluated in two separate studies. The first study (Study 1) was a cross-sectional study designed to evaluate whether patients with chronic hepatitis C infection have

lower serum lipid levels than matched uninfected controls. Thus, two groups of patients with (HCV Group) and without hepatitis C infection (Uninfected Control Group) and available lipid data were constructed.

Once the findings of Study 1 were known, we then sought to determine whether treatment-induced clearance of hepatitis C infection results in a rise in serum lipid levels when compared to lipid levels in subject who failed to clear the hepatitis C virus. For this question, we conducted Study 2, a retrospective cohort study consisting of patients with HCV who had lipid data available prior to and following HCV therapy (Treated HCV Group).

Study 1: Cross-Sectional Study

The HCV group was derived from the medical records of 2212 subjects with chronic hepatitis C from a database of Massachusetts General Hospital Gastroenterology clinic visits between 1997 and 2008. The HCV Group consisted of subjects 18 years of age or older with chronic hepatitis C, defined as documented positive HCV antibody and detectable HCV RNA. All subjects had fasting serum lipid panels available and none were undergoing hepatitis C treatment at the time of the study.

In the HCV Group, subjects with biopsy-proven or clinical evidence of cirrhosis, human immunodeficiency virus, hepatitis B infection, hemochromatosis defined by a pre-existing diagnosis of hemochromatosis or a positive HFE gene mutation or recipients of solid organ transplants were excluded. In addition, all patients who were on lipid lowering medications were excluded. Cirrhosis was defined by Ishak stage 5–6 fibrosis on biopsy or by clinical evidence of cirrhosis, determined by the presence of portal hypertension, defined by esophageal or gastric varices on endoscopy, ascites or splenomegaly or evidence of synthetic dysfunction on laboratory evaluation.

The Uninfected Control Group was derived from the National Health and Nutrition Examination Survey 2003–2004 (NHANES) cohort. NHANES is a national survey conducted by the National Center for Health Statistics that collects health and nutrition information via interviews and physical exams on a representative sample of the American population. One hundred and eighty uninfected subjects from NHANES 2003–2004 were matched to the HCV Group for age. Patients with positive anti-HCV antibody, hepatitis B surface antigen, anti-HIV antibody, other liver disease, hemochromatosis, previous liver or kidney transplantation or on lipid lowering medications were excluded.

The primary outcomes of interest were mean fasting LDL, cholesterol, HDL and triglyceride levels in the HCV Group and Uninfected Control Group.

Study 2: Retrospective Cohort Study

For Study 2, a Treated HCV Group was analyzed. The Treated HCV Group was derived from the medical records of 2212 subjects with chronic hepatitis C from a database of Massachusetts General Hospital Gastroenterology clinic visits between 1997 and 2008. Seven hundred eleven patients (32%) underwent hepatitis C treatment during this time. The Treated HCV Group consisted of subjects 18 years of age or older with chronic hepatitis C,

defined as documented positive HCV antibody and detectable HCV RNA. All patients had paired lipid panels, one within 12 months of treatment initiation and within 12 months following treatment completion. These levels were drawn by the patients' primary physicians as part of routine primary care.

In the Treated HCV Group subjects with biopsy-proven or clinical cirrhosis (as defined above), human immunodeficiency virus, hepatitis B infection, hemochromatosis defined by a pre-existing diagnosis of hemochromatosis or a positive HFE gene mutation or recipients of solid organ transplants were excluded. In addition, all patients who were on lipid lowering medications were excluded.

For the Treated HCV Group, sustained virologic response was defined as an undetectable HCV RNA six months following completion of therapy. Relapse was defined as initial clearance of HCV RNA at the end of treatment but detectable HCV RNA following cessation of treatment. Non-response was defined as failure to clear HCV RNA during therapy.

The primary outcomes of interest in Study 2 were mean pre and post treatment LDL, cholesterol, HDL and triglyceride levels in responders and non-responder/relapsers and change in LDL, cholesterol, HDL and triglycerides following treatment in the patients who achieved SVR when compared to non-responders or relapsers.

Additional covariates for both Study 1 and Study 2 collected included patient age, gender, HCV genotype, baseline HCV RNA level, concurrent medications, presence of diabetes mellitus, liver biopsy results including histologic activity index (HAI), steatosis score and fibrosis stage, patient weight and height when available and the diagnosis of coronary heart disease (CHD). CHD was defined by cardiac catheterization requiring intervention, coronary artery bypass graft surgery or the presence of a cardiac stress test positive for ischemia prompting subsequent medical management for coronary heart disease. Hepatitis C RNA level was tested using the COBAS® Amplicor version 2.0.

All statistical analysis was performed using SAS software, version V.9.13 (SAS Institute, Cary, NC). Continuous variables were analyzed using a Student's t-Test while categorical variables were analyzed using a Chi square test. Fisher's exact test was used to analyze Brunt Steatosis Scores and Wilcoxon rank sum test was used for the hepatic activity index. Groups 1 and 2 were age matched and univariate analysis was performed to evaluate the relationship between lipid levels and HCV status. Multivariate modeling was performed to determine the effect of sex, body mass index (BMI) and race on lipid levels for the case-control study. For the retrospective cohort study multivariate modeling was performed to determine the effect of age, sex and genotype on outcomes.

This study was approved by the Partners Human Research Committee.

Results

Study 1: Comparison of Lipids in Infected and Uninfected Subjects

Baseline Characteristics of the HCV and Uninfected Control Groups—One hundred and seventy-nine subjects with chronic hepatitis C infection from the MGH Hepatology Clinic and 180 subjects without hepatitis C infection from the NHANES 2003–2004 were compiled (Table 1). Subjects were matched 1:1 by age. Men comprised 47.5% of patients in the HCV Group and 48.3% in the Uninfected Control Group. The groups differed somewhat in the distribution of race. The HCV Group was 78.8% white, 10.6% black, 5.6% Hispanic and 5% Asian or other (the coding convention of NHANES). In the Uninfected Control Group, 52.2% of patients were white, 23.3% Hispanic, 18.9% black and 5.6% Asian or other. The mean age of the HCV Group was 52 years and of the Uninfected Control Group was 51.5 years. The mean BMI in both groups was 29.

Genotype 1 accounted for 65.4% of the HCV Group, genotype 2 12.8%, genotype 3 10.1%, genotype 4 1.6%, with unavailable genotype in 5.6% of patients. One hundred thirty seven patients underwent liver biopsies (76.5%). Sixty-one percent of the HCV Group were Ishak fibrosis stage 0–2 while the remaining 39.9% were stage 3–4.

HCV Infection is associated with lower LDL and total cholesterol levels (Table 2)—Patients in the HCV Group had significantly lower total cholesterol levels (mean 174 mg/dL) than the Uninfected Control Group (204 mg/dL). This difference remained significant when adjusted for sex, race and BMI ($p<0.0001$). Patients in the HCV Group also had significantly lower total LDL levels when compared to the Uninfected Control Group (94.3 mg/dL vs 120.8 mg/dL; $p<0.0001$) which also remained significant when adjusted for sex, race and BMI ($p<0.0001$) (Table 2).

HDL and triglyceride levels were not statistically significant between the HCV group and uninfected controls (Table 2).

In a subgroup analysis by genotype, patients with HCV genotype 3 had significantly lower total cholesterol levels than those with other genotypes ($p=0.0105$). Patients with genotype 3 also had a lower LDL level than those with Genotype 1 or 2 although the difference did not reach statistical significance ($p=0.11$, $p=0.06$, respectively). Total cholesterol and LDL of patients with genotype 2 were not significantly different of those with patients with genotype 1. There were too few patients with genotype 4 infection to compare cholesterol levels. No significant differences in HDL or triglycerides were seen between genotypes.

Study 2: Comparison of Pre and Post Treatment Lipid Levels

Baseline Characteristics of the Treated HCV Group—Eighty-seven patients of 711 patients (12.2%) undergoing HCV therapy had lipid data available both before and after treatment and met study inclusion criteria. Thirty-nine patients achieved SVR, 30 were non-responders and 18 relapsed after an initial response to therapy. Because of the small numbers of relapsers, relapsers and non-responders were combined into a single group. All but two relapsers had post-treatment lipid drawn after a documented return of viremia. Lipids were drawn in relapsers a mean of 23.6 weeks after relapse. The two remaining

relapsers had lipid levels drawn between the cessation of therapy and the documented relapse, thus the status of their viremia was not known at the time of lipid measurements. Baseline characteristics of the patients achieving SVR and those experiencing non-response or relapse are indicated in Table 3. Patients who achieved SVR were significantly younger (47.1 years vs. 51.6 years, $p=0.05$) than the relapser/non-responder group. Men predominated in each group, comprising 66% and 60% of the responders and non-responder/relapsers respectively. Fifty-six percent of the responders and 75% of the non-responder/relapsers were genotype 1 ($p=0.13$). Ten percent of the responders and 14% of the non-responder/relapsers had diabetes mellitus. The mean BMI in the responder group was 27.6 and 30.6 in the non-responder/relapser group ($p=0.13$). Of 87 patients, 15 (17%) did not have biopsies but had no clinical evidence of cirrhosis as noted above. Thirty-two percent of the SVR group had fibrosis stage 0–2 and 61.3% had stage 3–4. Sixty-one percent of non-responders had stage 0–2 fibrosis and 39% had stage 3–4 fibrosis, a non-significant difference from responders ($p=0.1$). All but three patients received peginterferon and ribavirin for a minimum duration of 12 weeks. Of the remaining three, two received peginterferon monotherapy due to renal disease and one received interferon and ribavirin.

Lower LDL and Cholesterol Levels Are Seen in Treatment Responders—All patients had lipid levels checked within one year before starting HCV therapy and within one year after stopping therapy. Lipid levels were drawn a mean of 19.3 weeks before therapy initiation in the responder group and a mean of 25.9 weeks before therapy initiation in the non-responder/relapser group. Post-treatment lipid levels were drawn a mean of 27.9 weeks after therapy cessation in the responder group and 29.8 weeks after therapy cessation in the non-responder/relapser group.

The mean pre-treatment LDL, cholesterol, triglyceride and HDL levels did not differ significantly between the responder and non-responder/relapser groups (Table 4). Notably, the mean values of LDL and cholesterol are below the recommended levels for treatment with lipid lowering medications based on NCEP guidelines for primary prevention of atherosclerosis.

A significant change was seen in circulating lipid levels post-treatment between responders and non-responders/relapsers. Responders had significantly higher mean post-treatment cholesterol levels than non-responders (189.1 vs. 165.2, $p=0.03$) as well as significantly higher LDL levels (105.8 vs 89.9, $p=0.05$). Responders experienced a mean increase of 19.7 mg/dL in cholesterol level, while non-responders experienced a mean decrease of 4.5 mg/dL ($p=0.0045$). Responders also experienced a mean increase of 26.4 in LDL levels while non-responders had a decrease in LDL by 2.9 mg/dL ($p=0.0046$) (Table 5). These values differ minimally from the differences between mean values of LDL and cholesterol because a small number of patients had incomplete follow-up panels (lacking either cholesterol or LDL) and were excluded from this analysis. The difference in cholesterol and LDL between responders and non-responders remained significant when controlling for age, sex and genotype ($p=0.002$, $p=0.0007$ respectively). These differences in mean cholesterol and LDL levels were driven by moderate increases seen in the majority of patients rather than by large changes seen in the minority of patients for both LDL and cholesterol. No significant difference in the change of triglycerides or HDL was seen ($p=0.16$, $p=0.27$ respectively). As

expected responders had a significant improvement in both alanine aminotransferase and aspartate aminotransferase levels compared to non-responders (ALT 24.0 vs 105.0, $p<0.0001$, AST 26.8 vs 86.3, $p<0.0001$)

We evaluated whether patients in the non-responder group who experienced lowering of their cholesterol and LDL had an associated increase in HCV RNA. For those patients ($n=20$) who experienced decreased cholesterol and LDL levels over the study period there was no significant change in HCV RNA level ($p=0.16$, $p=0.48$ respectively).

Lipid Lowering Therapy is Underutilized in HCV Patients—Data from our institution demonstrates that patients with hepatitis C frequently do not receive treatment for hyperlipidemia.(12) National Cholesterol Education Program Adult Treatment Plan Guideline III (NCEP ATP-III) recommends that patients with coronary heart disease (CHD) or CHD equivalents be treated for a LDL $>100\text{mg/dL}$.(13) Patients with two or more major CHD risk factors (including cigarette smoking, hypertension, HDL <40 , family history of premature CHD or age greater than 45 in men or 55 in women) should be treated for a LDL $>130\text{ mg/dL}$. Patients without CHD, CHD equivalents or two or more major CHD risk factors require treatment for LDL $>160\text{ mg/dL}$.

The mean LDL in patients who achieved sustained virologic response was 105.8 mg/dl. This level of LDL requires lipid lowering therapy in patients with coronary heart disease (CHD) or CHD equivalents. None of our patients had previously diagnosed CAD and none required lipid lowering treatment prior to HCV therapy. However, five of the 39 patients (13%) had LDL increases to greater than 130 mg/dl, one of whom had LDL levels $>160\text{ mg/dL}$ following successful eradication of HCV. Each of these patients had 2 or more major risk factors for CHD and by NCEP ATP-III criteria would have warranted treatment for hyperlipidemia as primary prevention. None of these patients received lipid-lowering therapy after HCV treatment. The reasons were not clear from the available records. In contrast, 2 of the patients (4%) who were non-responders or relapsers and had 2 or more CHD risk factors experienced increases in their post-treatment lipids to clinically meaningful levels ($p=0.14$), as defined above by NCEP criteria.

Total cholesterol level is also a known risk factor for the development of coronary heart disease.(14) Total cholesterol level of 200 mg/dL or less is considered desirable by the NCEP-ATP III and levels above 200mg/dL carry a 44% increased risk of CHD when compared to levels below 200mg/dL.(13, 14) The patients who achieved SVR also had a mean post-treatment cholesterol of 189.1 mg/dL. However, thirty-three percent of patients who achieved SVR had cholesterol levels less than 200 mg/dL prior to treatment and cholesterol $>200\text{ mg/dL}$ following treatment, compared to 10% of non-responders ($p=0.01$), indicating possible development of increased risk in CHD for patients achieving SVR.

Discussion

These studies demonstrate in several contexts the association between hepatitis C infection and relative hypolipidemia. We demonstrate that, when compared to age matched uninfected

controls, patients with chronic hepatitis C infection have lower cholesterol and LDL levels. This association persists when controlled for sex, race, and BMI. We further strengthen this association by examining the change in lipid levels when hepatitis C is eradicated compared to patients who do not respond to treatment. Again, we observed that the clearance of hepatitis C, in this case by curative treatment, is associated with elevated LDL and cholesterol levels. Thus, the multiple lines of investigation in this study strengthen the association between HCV infection and hypolipidemia.

Our findings are consistent with other studies finding low circulating cholesterol and LDL levels in patients with chronic hepatitis C infection (11, 15, 16); our study extends these findings to an American, predominantly genotype 1 cohort, and does so in both a case-control and cohort manner. Our study did not find that pre-treatment lipid levels were predictive of treatment response. This is in contrast to the findings of Gopal et al., who found that higher pre-treatment cholesterol and LDL levels were associated with greater odds of achieving a SVR. (17) However, it is important to note that nearly half of patients (39.4%) in the Gopal study had a fibrosis stage of 3 or 4 (out of 4), indicating incomplete or complete cirrhosis. Cirrhosis is associated with both lower lipid levels and lower rates of treatment response and may have confounded the findings in this study.(18)

A unique strength of our study was the use of complete paired lipid data, evaluating LDL, cholesterol, triglycerides and HDL, before and after hepatitis C treatment allowing direct evaluation of change in serum lipids at the level of the individual subject in an American cohort. Additionally, our study excluded cirrhotic patients, who are known to have decreased serum lipid levels, thus eliminating the potentially confounding effect of cirrhosis. Finally, our study also excluded patients who were on lipid lowering therapy, another potential confounder.(18)

Our finding of a substantial portion of patients with meaningful increases in serum lipids with successful clearance of HCV has important implications for hyperlipidemia management. In our study 13% of patients who achieved SVR had increases in LDL to levels that warranted treatment based on the presence of 2 or more CHD risk factors and 33% had increases in cholesterol levels resulting in a significant risk in the development of coronary heart disease.(14) The percentage of patients with 2 or more CHD risk factors is likely an underestimate of the number of patients with 2 or more risk factors as few of the patients had any documented family history to evaluate for the presence of early CAD in family members and several lacked documented social history to determine whether they were tobacco users. However, none of these patients were placed on lipid lowering medications for the over one year after their elevated lipid panels were tested despite a lack of documented contraindications to HMG CoA Reductase inhibitors. With multiple studies demonstrating the benefit of lipid lowering for primary prevention of CHD, recognition of the development of post-HCV treatment hyperlipidemia may be important to reduce CHD mortality in this population.(19–21).

Our study does have several important limitations. While NHANES is designed to be a representative sample from the US population, the population of the HCV Group was derived from a tertiary referral center and thus our study compares two slightly different

populations especially in regards to ethnicity which was been shown to effect hepatitis C treatment outcomes. However, our cohorts were age matched and were similar in gender and BMI; in multivariate analysis we also controlled for differences in ethnicity seen between the two cohorts.

Second, Study 2 is retrospective in nature and thus limits the available data to assess for confounding variables. For example, pre and post treatment weights were not available for each patient and it is conceivable that a differential weight loss between responders and non-responders could account for the difference in post-treatment LDL and cholesterol. However, Seyam et al., have demonstrated that there is not a significant difference in weight loss between responders and non-responders.(22) Furthermore, their study demonstrated that median body weight returned to baseline six months following the cessation of therapy. The mean time of lipid sampling in our cohort was 28 weeks post-cessation of therapy in responders and 30 weeks post-cessation in non-responders/relapsers. Thus, we would expect that our patients had returned to their baseline weight at the time of their lipid testing.

Additionally, we cannot exclude an influence of interferon therapy on the lipid perturbations seen in our treated patients. Soardo et al., found changes in HDL, apolipoprotein A-I and HDL3 after the initiation of interferon therapy, but no changes were noted in cholesterol and LDL levels.(23) In addition, with the post-treatment lipid panels drawn more than 6 months following the cessation of treatment the influence of interferon on host lipids would likely be minimal. Finally, even if therapy had influenced lipid levels, the observed differences between responders or non-responders controlled for therapy, which was received by both groups.

Our study also combined non-responders and relapsers into a single group. We would expect that prior to relapse and return of active HCV replication, relapsers would have similar LDL and cholesterol levels to responders and should be grouped with responders. However, 89% of our relapsers had relapsed at the time of lipid measurement with only two patients having had lipids measured before documented relapse. Thus, the relapsers had ongoing viral replication similar to that of non-responders and might be predicted to have similar lipid metabolism. However, larger studies of both relapsers and non-responders will be necessary to confirm this finding.

Finally, we found no significant difference in HCV RNA levels as LDL and cholesterol levels decreased in non-responders. However, this analysis was significantly limited by small numbers of patients and by the measurement of HCV RNA levels which were often reported as greater than 500,000 or 700,000.

Our findings may be explained through an understanding of the similarities between HCV replication and HMGR inhibitors effects on cholesterol and LDL levels. HMGR inhibitors inhibit the second step in the mevalonate cholesterol synthesis pathway, the conversion of HMG CoA to mevalonate. This inhibition of mevalonate production inhibits cholesterol synthesis and decreases the concentration of cholesterol esters available for very low density lipoproteins (VLDL) to deliver via the circulation to the periphery. Hepatocytes still require cholesterol for multiple cellular functions; thus, when cholesterol synthesis is

downregulated, hepatocytes compensate by upregulating LDL receptors to increase LDL uptake and ultimately the availability of intracellular cholesterol. (24) In this manner HMGR inhibitors decrease hepatic cholesterol synthesis and both circulating cholesterol and LDL levels.

Based on our findings, we propose a model by which HCV replication may produce effects similar to those observed with HMGR inhibitors. HCV replication could decrease intrahepatic cholesterol synthesis through two possible pathways; first, it may shunt geranylpyrophosphate, out of the mevalonate pathway, decreasing the quantity of this necessary intermediate available for cholesterol synthesis. Second, it may divert cholesterol to the synthesis of intracellular membranes that are necessary for the viral replication complex. The net effect of these diversions is the decrease of available cholesterol for physiologic intracellular processes and for peripheral delivery via VLDL, ultimately resulting in decreased serum cholesterol levels. The decrease in available intracellular cholesterol may also lead to an increase in LDL receptors and intrahepatic LDL. This increase in LDL uptake may account for the decreased serum LDL levels in HCV infection. Under this model, as was observed in our study, successful elimination of HCV would be predicted to remove these diversions, and result in rebound of circulating cholesterol and LDL levels.

Our study has several important implications. First, HCV infection is associated with lowering of host lipids, providing further evidence of an important interaction between HCV and host lipids, and suggesting a possible novel therapeutic target. Second, post-treatment viral clearance is associated with increased LDL and cholesterol, often to levels associated with an increased risk of coronary heart disease. We suggest that serum lipid levels should be assessed in follow-up among patients undergoing successful antiviral therapy, as clearance may reveal some patients with previously unappreciated coronary risk. Further research is needed to correlate the rise in lipid levels with clinically significant outcomes, such as the development of coronary heart disease.

Acknowledgments

Financial Support: KEC receives support from Bristol-Myer-Squibb Virology Fellowship. RTC receives grant support from Roche Laboratories and Schering-Plough.

List of Abbreviations

LDL	low density lipoprotein
SVR	sustained virologic response
HCV	hepatitis C virus
NHANES	National Health and Nutrition Examination Survey
HAI	histologic activity index
NCEP ATP-III	National Cholesterol Education Program Adult Treatment Plan Guideline III

CHD	coronary heart disease
RNA	Ribonucleic acid
BMI	body mass index
HMGR	HMG Co-A reductase

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Table 1

Baseline Characteristics of the HCV and Uninfected Control Groups

	HCV Group	Uninfected Control Group	P Value
N	179	180	
Gender (men/women)	85/94	87/93	0.83
White/Black/Asian [*] /Hispanic	141/19/9/10	94/34/10/42	p<0.0001
Mean Age (SD)	52 (+/-10.9)	52 (+/-13.8)	0.41
BMI Mean (SD)	29 (+/-6.8)	29 (+/-6.6)	0.88
Genotype 1	117 (65.4%)	---	
Genotype 2	23 (12.8%)	---	
Genotype 3	18 (10.1%)	---	
Genotype 4	3 (1.6%)	---	
Genotype NR	18 (5.7%)	---	
Median Ishak Hepatic Activity Index (Range)	5 (0-11)	---	
Moderate to Severe Steatosis (%) ^{**}	8 (4.4%)	---	
Ishak Fibrosis Stage ^{***}			
Stage 0-2	74 (60.1%)	---	
Stage 3-4	49 (39.9%)		

^{*} Coded in NHANES cohort as "Asian or Other"

^{**} Brunt Steatosis Score 3-4

^{***} Patients with Ishak Fibrosis Score of 5 or 6 were excluded

Table 2

Mean Lipid Values for the HCV and Uninfected Control Groups

	HCV Group	Uninfected Control Group	P value
Cholesterol (SD)	173.6 (+/-42.2)	204.2 (+/-39.7)	<0.0001
LDL (SD)	94.3 (+/-32.6)	120.8 (+/-34.4)	<0.0001
HDL (SD)	53.9 (+/-18.5)	53.8 (+/-13.9)	0.9621
Triglycerides (SD)	130.2 (+/-82.6)	137.6 (+/-72.9)	0.3373

Table 3

Baseline Characteristics of Treated HCV Group: Chronic Hepatitis C Patients Treated with Antiviral Therapy

	Sustained Virologic Responders	Non-Responders/ Relapsers	P value
N	39	48	
Mean Age (SD)	47.1(+/-11.8)	51.6 (+/- 9.0)	0.05
Gender (men/women)	26/13	29/19	0.55
Mean BMI (SD)	27.6 +/-5.5	30.6 +/- 5.4	0.13
Baseline HCV RNA (IU/mL) (SD)	827,531.595(+/-1362749.9)	579,414.511(+/-213455.1)	0.22
Genotype 1/2/3/4/unknown	22/10 /5/1/1	37/5/3/3/0	0.13
Diabetes Mellitus	4 (10.53%)	7 (14.5%)	0.56
Median Ishak HAI Score (Range)	5 (3–10)	4 (1–9)	0.08
Moderate to Severe Steatosis (%) [*]	1 (2.7%)	1 (2.6%)	1.0
Ishak Fibrosis Stage			
Stage 0–2 (%) ^{**}	12 (38.7%)	25 (61.0%)	0.10
Stage 3–4 (%) ^{**}	19 (61.3%)	16 (39.0%)	

* Brunt Steatosis Score 3–4

** Ishak Fibrosis Stage 5–6 were excluded from this study

Table 4

Mean Pre and Post-Treatment Lipid Levels for Responders and Non-Responder/Relapsers

	Sustained Virologic Response		Non-Responders/Relapsers		P Value for comparison of pre-treatment values & post-treatment values	
	Pre-Treatment	Post-Treatment	Pre-Treatment	Post-Treatment	Pre-Treatment	Post-Treatment
Cholesterol	173.2	189.1	169.0	165.2	0.62	0.003
LDL	97.1	105.8	90.8	89.9	0.40	0.05
Triglycerides	158.4	145.9	141.0	151.3	0.54	0.90
HDL	50.9	51.6	50.8	48.3	0.98	0.39

Table 5

Differences in Pre-Treatment and Post-Treatment Paired Cholesterol and LDL Levels in Responders and Non-Responder/Relapsers*

	Sustained Virologic Response	Non-Responders/Relapsers	P Value
Cholesterol (SD)	+19.7+/-49.2	-4.5+/-25.1	0.0045
LDL (SD)	+26.4 +/-49.1	-2.9+/-39.4	0.0046

* These values differ minimally from the differences in Table 4 as small number of patients had incomplete follow-up panels and were excluded from this analysis.