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Impact of Insulin Resistance and Lipid Profile Abnormalities on Virological Response to Treatment of Hepatitis C Virus

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Recent studies suggested that virological response of Hepatitis C Virus to treatment might be lower insulin resistance (IR) and lipid profile abnormalities, but the extent of their impact on treatment response has not been established. The aim of this study was to confirm the role of IR and lipid profile abnormalities on virological response of chronic hepatitis C infected patients and to determine its magnitude. Eighty non-hypertensive, non-cirrhotic Saudi patients with chronic HCV infection; Patients were divided in to two equal groups according to their blood level profile and insulin resistance levels: Group (A): Included HCV patients with normal lipid profile and non-diabetic without insulin resistance. Group (B): Included HCV patients with high Triglycerides, Total cholesterol and LDL & non-insulin dependent diabetic with insulin resistance. There were significant differences between both groups regarding Total cholesterol, Low density lipoprotein, High density lipoprotein, insulin resistance and virological response. The Pearson's correlation coefficients test for the relationship between virological response and Total cholesterol, Low density lipoprotein, High density lipoprotein, insulin resistance in both groups showed a strong direct relationship in both groups. While, there was a strong inverse relationship between virological response and High density lipoprotein in both groups. Insulin resistance and lipid profile abnormalities adversely affect virological response to treatment of Hepatitis C Virus.

Key words: Insulin Resistance; Blood Lipids; Virologic Response; Chronic Hepatitis C.

Hepatitis C virus (HCV) chronically infects around 170 million people worldwide. The treatment for chronic hepatitis C virus (CHC) has been combination pegylated interferon-á and ribavirin (PR)[1].

Chronic hepatitis C (CHC) infection, usually an asymptomatic infection, has long-term serious complications such as cirrhosis, hepatocellular carcinoma, and end-stage liver disease requiring liver transplantation (LT). Despite the development of new anti-hepatitis C virus (HCV) drugs, ribavirin (RBV) remains the single most important drug to prevent relapse and is frequently included among newer regimens being developed with novel small molecule anti-HCV drugs. The current approved treatment is a combination therapy of once weekly subcutaneous pegylated-interferon (PEG-IFN)-α plus body-weight-based oral RBV regimen[2].

A large amount of evidence suggests that chronic hepatitis C is a systemic disease, leading to metabolic sequelae due to the interaction of the hepatitis C virus (HCV) with lipid and glucose metabolism, resulting in hepatic steatosis, insulin resistance, type 2 diabetes, and hypocholesterolemia, all common features in this setting of patients[3].

HCV infection is an independent risk factor for diabetes development[4], HCV-genotypes 1 and 4 and their viral load are associated with insulin resistance[5], and in vivo human studies showed that HCV induce both liver and peripheral insulin resistance[6]. This has prompted speculation that HCV, via different molecular mechanisms (up-regulation of tumour necrosis factor-α (TNF-α),

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down-regulation of suppressor of cytokine signalling, and the protein phosphatase PPA2), is able to affect insulin signaling and as a result induces insulin resistance[7].

HCV partices in the circulation are associated with lipoproteins. Association with lipoproteins of varying triglyceride and cholesterol composition determines the density distribution of HCV RNA in plasma[8]. Blood lipids concentration is an independent predictor of SVR to dual peginterferon-α- ribavirin therapy in HCV-genotype 1[9-11]. Interestingly, LDLC remained a significant independent predictor of SVR in post hoc analysis of the telaprevir-based REALIZE trial[12].

As hypertriglyceridemia, elevated low-density lipoprotein cholesterol (LDL-C) and low HDL-cholesterol are related to insulin resistance in non-diabetic subjects[13]. Also, insulin resistance was associated with indices of obesity and an atherogenic lipid and hyperglycaemic profile in oland in obese adolescents[15]. The aim of this study was to confirm the role of IR and lipid profile abnormalities on virological response of chronic hepatitis C infected patients and to determine its magnitude.

Subjects and Methods

Eighty non-hypertensive, non-cirrhotic Saudi patients with chronic HCV infection; among these cases 40 patients have normal lipid profile and non-diabetic, where the other 40 patients have high cholesterol, triglycerides and LDL levels and non-insulin dependant diabetic patients with insulin resistance, their age ranged from 30 to 55 (35.87 ± 4.21) years, were studied on referral to Gastroenterology and Hepatology Department, King Abdulaziz University Teaching Hospital, Saudi Arabia. All these patients were anti HCV positive by enzyme-linked immunosorbent assay (ELISA). None of the patients included in this study had other potential causes of liver disease, such as alcoholism or autoimmune phenomena. All the patients were not treated previously with antiviral drugs. Only patients diagnosed with chronic HCV mono-infection and have anti HCV antibodies by ELISA were selected to undergo Real-Time polymerase chain reaction (RT-PCR) and were treated with combined pegylatedinterferon--alfa (PEG-IFNα)-ribavirin therapy. This study was approved by the Scientific Research Ethical Committee, Faculty of Applied Medical Sciences at King Abdulaziz University. All participants were free to withdraw from the study at any time. If any adverse effects had occurred, the experiment will be terminated and the Human Subjects Review Board will be informed. However, no adverse effects occurred, and so the data of all the participants were available for analysis.

Patients were divided in to two equal groups according to their blood level profile and insulin resistance levels

Group (A)

Included forty HCV patients with normal lipid profile and non-diabetic without insulin resistance.

Group (B)

Included forty HCV patients with high Triglycerides, Total cholesterol and LDL & non-insulin dependent diabetic with insulin resistance.

Methods

Evaluated Parameters

Real-Time polymerase chain reaction (RT-PCR)

Ten milliliter blood samples were collected from each participant at study entry. The blood samples were obtained using disposable needles and heparinized vacuum syringes and stored at –70°C until assayed. Serum samples of all participants were tested for Real-Time polymerase chain reaction (RT-PCR) to detect serum HCV RNA levels by polymerase chain reaction using the COBAS TaqMan HCV test, v2.0 (Roche Diagnostics, Indianapolis, NJ, USA).

Blood lipid profile and Insulin resistance measurements

Blood sample after fasting for 12 hours was taken from each women in clean tubes containing few mg of K2EDTA, centrifuged and plasma was separated and stored frozen at -20° used for estimation of plasma lipid profile includes Triglycerides, Total cholesterol and LDL. Also, Homeostasis Model Assessment-Insulin Resistance (HOMA) index for insulin sensitivity was computed following this equation: [fasting glycemia (mmol/L) · fasting insulin (mIU/L)]/22.5[16].

RESULTS

Eighty Saudi patients with chronic HCV infection were studied on referral to Gastroenterology and Hepatology Department,

King Abdulaziz University Teaching Hospital, all these patients were anti HCV positive by enzyme-linked immunosorbent assay (ELISA). Patient characteristics were homogeneous when grouped into group (A) Included forty HCV patients with normal lipid profile and non-diabetic without insulin resistance and group (B) Included forty HCV patients with high Triglycerides, Total cholesterol and LDL & non-insulin dependent diabetic with insulin resistance (table 1).

There were significant differences between both groups regarding Total cholesterol, Low density lipoprotein, High density lipoprotein, insulin resistance and virological response (Table 2). The Pearson's correlation coefficients test for the relationship between virological response and Total cholesterol, Low density lipoprotein, High density lipoprotein, insulin resistance in both groups showed a strong direct relationship in both groups (Table 3, 4). While, there was a strong inverse relationship between virological response and High density lipoprotein in both groups (Table 3, 4).

Table 1. Patient characteristics

	Mean ± SD		Significance
	Group (A)	Group (B)	
Age (year)	45.43± 8.96	46.62± 7.58	P > 0.05
BMI (kg/m^2)	30.15 ± 3.12	30.64 ±3.45	P > 0.05
WBC, /mm^3	4830 ± 210.13	4880 ± 240.56	P > 0.05
Platelets (10^3/cmm)	167.32± 34.16	163.75± 38.62	P > 0.05
Hb (gm/dl)	12.55± 1.27	12.04± 1.12	P > 0.05
Albumin (gm/dl)	3.51± 0.73	3.49± 0.68	P > 0.05
Total Bilirubin (mg/dl)	1.22± 0.78	1.16± 0.97	P > 0.05

BMI = Body Mass Index Hb = Haemoglobin WBC = White Blood Cells

Table 2. Mean value and significance of Total cholesterol, LDL, HOMA-IR and virological response of group (A)

	Mean ± SD		Significance
	Group (A)	Group (B)	
Cholesterol (mg/dL)	165.32 ± 25.27	242.65 ± 27.92	P < 0.05
LDL (mg/dL)	97.35± 15.13	170.85± 14.17	P < 0.05
HDL (mg/dl)	38.95±3.87	34.61±3.54	P < 0.05
HOMA-IR	5.82 ±1.31	8.91± 1.25	P < 0.05
HCV-RNA (KIU/mL)	1225.34± 204.62	4488.65± 86.13	P < 0.05

LDL= Low Density Lipoprotein HDL= High Density Lipoprotein
HOMA-IR = Homeostasis Insulin Resistance Index

Table 3. Shows the Pearson's correlation coefficients test value and the relationship between the virological response and Total cholesterol, Low density lipoprotein, insulin resistance in group (A)

Test	Pearson's value	Relationship to virological response
Total cholesterol	0.91	Strong direct relationship
Low density lipoprotein	0.90	Strong direct relationship
High density lipoprotein	-0.88	Strong inverse relationship
Insulin resistance	0.93	Strong direct relationship

Table 4. Shows the Pearson's correlation coefficients test value and the relationship between the virological response and Total cholesterol, Low density lipoprotein, insulin resistance in group (B)

Test	Pearson's value	Relationship to virological response
Total cholesterol	0.90	Strong direct relationship
Low density lipoprotein	0.89	Strong direct relationship
High density lipoprotein	-0.86	Strong inverse relationship
Insulin resistance	0.91	Strong direct relationship

DISCUSSION

In our study, patients with high cholesterol level, high LDL level, low HDL level and insulin resistance showed a higher virological response than patients with normal lipid profile and no insulin resistance, also there was a strong direct relationship between insulin resistance and lipid profile abnormalities on virological response to treatment of Hepatitis C Virus. Our finding were compatible with the results of many previous studies as Ramcharran et al., who showed in his study that there is a direct relationship between LDL and SVR that may partially be explained by competition for LDL receptor sites preventing viral entry into hepatocytes, increasing exposure of HCV to the host immune response in the serum[17]. Similar results were also obtained from the study of Gopal et al., showed that having higher serum LDL and cholesterol levels before treatment may be significant prognostic indicators for treatment outcome of those with chronic hepatitis C infection[9].

Also, Martinot-Peignoux etal., observed that low levels of LDL cholesterol were associated with advanced fibrosis and high HCV viral load, both being predictors for poor response to interferon therapy[18]. However, Harrison et al., found that in their study on 1464 patients with baseline elevated LDL levels or low HDL levels; the SVR rate was significantly higher than that in patients with normal levels (44.9% versus 34.0%)[11].

Concerning the virological response and insulin resistance (IR), experimental and clinical data suggest that HCV infection itself may promote IR[5]. In large cohort studies, the prevalence of diabetes in patients with chronic hepatitis C ranges from 20% to 50%[5]. Many studies have shown that the baseline HOMA-IR index is another major predictor of the response to Peg-IFN and ribavirin[19-23]. Thus, IR could be introduced as a marker predictive of SVR. However, Sustained virological response is the surrogate marker used by most studies to evaluate the effectiveness of therapy and is associated with improved outcomes, such as low likelihood of viral relapse, reduced mortality, and reduced risk of cirrhosis and hepatocellular carcinoma[24].

Although it is well established that IR negatively affects the probability of reaching a SVR, some studies did not find such an association[25-29]. In some of them, this may have been due to their small sample size. As a result, the magnitude of the impact of IR on treatment response remains unsettled and rigorous analysis of all available data from all studies is required. HCV patients with IR have a 20% lower SVR than patients without IR. The baseline HOMA-IR index is a major determinant of SVR[30].

Also Giordanino et al. reported data on a retrospective study of 309 patients with CHC, treated with dual antiviral therapy, and followed for 11.0 ± 4.9 years, evaluating the impact of diabetes on occurrence of liver-related events, diabetes-related events and mortality rates. As expected, they observed that diabetics have a higher number of diabetes- and liver-related events than non-diabetics (10% vs. 1.5%, p = 0.006; 18% vs. 5.7%, p = 0.007, respectively) with a mortality of 14% vs. 1.5% (p = 0.0003). However only baseline cirrhosis and non-SVR were independent risk factors for liver events, while diabetes was an independent factor for diabetes-related events. These data are very interesting, and although they do not document a direct role of diabetes in liver events; considering the high prevalence of cirrhosis and non-SVR among diabetic HCV patients, they could suggest an indirect role of

diabetes and underlying insulin resistance in liver disease progression and in lack of SVR, finally resulting in a high risk of liver events[31].

Recent clinical studies in European[23] and both African-American and Caucasian-American[32] genotype 1 patients observed that insulin resistance impaired SVR to dual therapy, and similar results were observed for patients with HCV genotype 2 or genotype 3 infection[33] , and in those with HCV genotype 4 [34]. In line with these observations, diabetes also appears to be a negative SVR predictor, and a recent meta-analysis showed that HCV patients with insulin resistance have a 20% lower SVR than those without insulin resistance [30].

CONCLUSION

Insulin resistance and lipid profile abnormalities adversely affect virological response to anti-viral treatment of Hepatitis C Virus, so an integrated treatment approach is essential to correct the insulin resistance and lipid profile abnormalities through medications, life style change and exercise training program.

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