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ORIGINAL ARTICLE

Insulin resistance: a predictor for response to interferon-based therapy in Egyptian patients with chronic HCV genotype 4

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Abstract Egypt has the highest worldwide hepatitis C virus infection (HCV), it estimated about 13.8 %. Interferon alpha is considered the backbone for any effective treatment. These therapies are not without adverse effects nor are they always cost effective. Accordingly, it is important to identify patients with a considerable chance of response before initiation of therapy. Rapid virological response (RVR) is important for identification of non-responders permitting therapy discontinuation and avoiding adverse effects and costs. Evaluate the reliability of homeostasis model assessment (HOMA) method in prediction of HCV treatment response among Egyptian patients with chronic HCV genotype 4 infections. Our study included 80 participants; 50 non-cirrhotic non-diabetic patients with chronic HCV genotype 4 (group I), and 30 age- and sex-matched patients negative for HCV RNA and consequently they did not receive hepatitis treatment at the time of sampling (group II) were included. According to HOMA score, group I was further divided into group Ia with insulin resistance (IR) >2.5 (36 %) and group Ib with IR <2.5 (64 %). HOMA-IR was significantly associated with high RVR, progressive fibrosis stages, high pretreatment ALT levels, and body mass index. Our data suggests that IR strongly affects VR. HOMA-IR would appear to be useful in predicting RVR and should be evaluated at baseline in all chronic HCV patients before initiating interferon therapy to reduce unnecessary and ineffective treatments and enhance cost effectiveness of treatment.

Keywords HCV · Insulin resistance · HOMA · RVR · Interferon · Genotype 4

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Introduction

Hepatitis C virus infection (HCV) infection is a leading cause of chronic liver disease. More than 3 % of the world's populations (around 170 million people) are infected and about 130 million are at risk of cirrhosis (Lauer and Walker 2001). Egypt has one of the highest HCV prevalence in the world (nearly 15 %) of its population. Genotype 4 comprises 93 % of the total HCV cases in Egypt; other genotypes comprise only small proportions of the infected population (Zekri et al. 2009). Egyptian populations' encountered an increasing prevalence of type 2 diabetes mellitus (T2DM). HCV infection is associated with the development of insulin resistance (IR) and, consequently T2DM (Zein et al. 2000; Kobashi-Margáin et al. 2010). IR 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. IR results in increase of insulin secretion when insulin sensitivity decreases until a threshold in which insulin secretion did not induce improvement in insulin sensitivity and diabetic state emerges. In addition to T2DM, IR results in the increase of risk of life-threatening complications such as cardiovascular diseases, renal failure, and infections (Holstein et al. 2002) and might complicate HCV infection by a faster progression of fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma (HCC), and a poor response to antiviral therapy possibly by causing interferon resistance (Méndez-Sánchez et al. 2007; Hung et al. 2010; Romero-Gómez et al. 2005).

IR could be caused in the general population by lack of exercise, overeating, and obesity. Indeed in patients with HCV infection, hepatic inflammation-activated inflammatory cytokines, and HCV-induced impairments of insulin and lipid signaling molecules are important factors for the development IR (Maeno et al. 2003). IR could be explained by direct damage of the pancreatic tissue by HCV core proteins (Shintani et al. 2004; Kawaguchi et al. 2005). All HCV genotypes can induce IR; however, different HCV genotypes show characteristic variations in their pathological properties, people with genotype 1 or 4 are more prone than those with genotype 3 to develop IR (Moucari et al. 2008). Thus, HCV-associated IR is a therapeutic target at any stage of HCV infection. Association between use of exogenous insulin or a sulfonylurea agent and the development of HCC has recently been reported. On the other hand, insulin-sensitizing agents are reported to improve sustained virologic response rates (Kawaguchi and Sata 2010). Our study evaluated the reliability of homeostasis model assessment (HOMA) method in prediction of HCV treatment response among Egyptian patients with chronic HCV genotype 4 infections.

Patients and methods

The present work was conducted on a total number of 80 participants. Fifty non-diabetic non-cirrhotic Egyptian naïve chronic HCV-infected patients genotype 4 (group I) were included. They were 30 males (60 %) and 20 females (40 %). Age of patients ranged from 40 to 49 years with mean value of 45.23±2.75 years. All patients were legible to receive interferon- and ribavirin-based therapy. Thirty age- and sex-matched patients negative for HCV RNA and consequently did not receive hepatitis treatment at the time of sampling were selected as controls (group II). They were 18 males (60 %) and 12 females (40 %). Their ages ranged from 45 to 52 years with mean value of 46.32±4.35. According to HOMA-IR score group I was subdivided into group Ia with insulin resistance (IR)>2.5 and group Ib with IR<2.5. Patients were selected among cases referred from Hepatology Outpatient Clinic in Kasr El-Aini hospitals; a written informed consent was taken from all patients. Inclusion criteria included positivity for anti-HCV (fourth-generation enzyme immunoassay, age >18 and <60 years old and liver fibrosis grade (Metavir stage F2–F4)). Exclusion criteria included decompensated liver disease, co-infection with HBV or HIV, autoimmune disorders, clinically significant cardiac abnormalities, renal impairment, pregnancy and breast feeding, hypersensitivity to peg-interferon alpha and ribavirin, hemoglobinopathy, and diabetes mellitus.

All patients were subjected to clinical history and examination, laboratory analysis including CBC, PC, ALT, AST, GGT, ALP, total bilirubin, serum albumin, urea and creatinine, fasting blood sugar and fasting insulin and HBA1C (measured by a two-site immunoenzymometic assay (ST-AIA-PACK IRI, Tosoh corporation, Tokyo, Japan)), anti-HCV antibodies in sera of patients and controls were estimated using fourth-generation enzyme-linked immunosorbant assay according to the manufacturer's instructions (Abbott). Real-time quantitative PCR for quantitative estimation of HCV viral load (amplicor monitor HCV v.2; Roche molecular systems, Mannheim, Germany; low viremia was defined as viral load lower than 100×10^3 IU/L, moderate viremia as viral load 100–1,000$\times10^3$ IU/L, and high viremia when viral load >1,000$\times10^3$ IU/L); HCV genotyping was determined using INNO-LiPAII and III versant Kit (Innogenetics, Ghent, Belgium) according to manufacturer's directions. Hepatitis B surface antigen, anti-hepatitis B core antibody, and anti-HIV were tested using commercially available kits for exclusion of co-infection with HBV or HIV infection. Insulin resistance was determined by HOMA method using the following equation: HOMA-IR=fasting glucose (milligrams per deciliter)×fasting insulin (micro international units per milliliter)/405(Matthews et al. 1985). Abdominal ultrasound and liver biopsy were done for assessment of fibrosis. Finally, measurement of basal IR using HOMA method was done, cut-off value was 2.5, values above 2.5 means IR and below it there was no significant IR. Group I was further divided into two subgroups according to IR: group 1a included 18 cases with HOMA-IR >2.5 (36 %) and group Ib included 32 cases with HOMA-IR <2.5 (64 %). Patients of group I were then treated with peginterferon (peg-IFN; Schering-Plough K.K, Kenilworth, NJ), which was given in weekly doses adjusted to body weight according to manufacturer's instructions, and 1.5 micg/kg/week plus ribavirin (rebetol; Schering-Plough K.K.), which was given in daily doses adjusted to body weight (800 mg for weights<50 kg, 1,000 mg for weights 50–60 kg, 1,200 mg for weights 65–80 kg, and 1,400 mg for weights>80 kg). During treatment, patients were evaluated to monitor compliance and side effects by weekly assessment of CBC, ALT and AST in the first month and then every 4 weeks up to the end of the treatment, then measurement of HCV-RNA at week 4 to evaluate rapid virological response (RVR).

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 16, SPSS inc. USA) and Microsoft Excel 2007. Results were expressed as mean ± SD. For quantitative data, comparison between two groups was undertaken using paired *T* test. Chi-square test (Fisher's exact test)

was used to examine relationships between qualitative variables. Pearson's correlation coefficients for the different variables were calculated. $P<0.05$ was considered significant. $P<0.001$ was considered highly significant.

Table 1 Clinical and laboratory data of both groups at diagnosis

Item	Group I	Group II	*P* value
Age (years)			
Range	40–49	45–52	0.16
Mean ± SD	45.24±2.755	46.32±4.35	NS
Sex (years)			
Males (no.; %)	30; 60 %	20; 66.7 %	0.4
Females (no.; %)	20; 40 %	10; 33.3 %	NS
Obesity			
Present (no.; %)	12; 24 %	9; 30 %	0.55
Absent (no.; %)	38; 76 %	21; 70 %	NS
BMI			
Range	22–27	22–25	0.57
Mean ± SD	24.06±0.688	23.98±0.488	NS
AST (U/L)			
Range	12–85	18–45	0.041
Mean ± SD	42.8±25.39	31.8±18.33	S
ALT (U/L)			
Range	11.9–95	14–55	0.03
Mean ± SD	45.40±26.97	33.12±19.22	S
GGT (U/L)			
Range	22–180	25–51	<0.001
Mean ± SD	64.48±42.08	31±16.55	HS
T.bilirubin (mg/dl)			
Range	0.4–4.8	0.25–0.95	<0.001
Mean ± SD	2.25±0.19	0.55±0.05	HS
S. albumin (g/dl)			
Range	1.8–4.2	3.5–4.8	<0.001
Mean ± SD	2.15±0.28	3.79±0.49	HS
F.B.S (mg/dl)			
Range	75–145	82–.120	0.093
Mean ± SD	125.21±38.9	110.91±32.01	NS
F. insulin (μIU/mL)			
Range	4.57–20	5.02–9.5	<0.001
Mean ± SD	11.14±3.81	4.89±1.02	HS
Insulin resistance			
Range	0.8–5.0	0.4–2.0	<0.001
Mean ± SD	2.65±0.09	1.18±0.05	HS
HBA1C (%)			
Range	4.2–6.8	4.8–6.2	0.04
Mean ± SD	5.35±0.73	5.02±0.65	S
HCV RNA baseline (copies/ml)			
Range	65,034–850,450	No viremia	–
Mean ± SD	230,556±2,400		
HCV RNA after 4 weeks (copies/ml)			
Range	0–325,000	No viremia	–
Mean ± SD	88,000±1,100		

NS non-significant, *S* significant, *HS* highly significant

Results

Clinical and laboratory data of all patients at the time of diagnosis are listed in Table 1. Group I patients in this study were subdivided into two groups based on baseline IR with cutoff HOMA-IR value ~2.5: group Ia included 18 cases (36 %) with HOMA-IR>2.5 and group Ib included 32 cases (64 %) with HOMA-IR <2.5. At a criterion value 2.47, the sensitivity of HOMA test for predicting RVR 90 %, and its specificity 100 % which indicates that it is a reliable test for predicting RVR.

HOMA-IR score >2.5 was significantly higher in chronic hepatitis C patients (CHC) with positive viral load than in control group (mean value 2.65±0.09 versus 1.18±0.05, $P<0.001$).

A strong positive correlation between HOMA-IR and RVR was elicited (higher HOMA-IR index was significantly associated with higher HCV viral load; $r=0.8272$, $P<0.05$; Fig. 1).

Comparison between both subgroups regarding HOMA-IR revealed a highly statistical significant difference with a higher mean value in group Ia than in group Ib (3.95± 0.4907 versus 1.7±0.5713, $P<0.001$; Table 2).

Comparison between both subgroups regarding HCV RNA levels after 4 weeks which reflect RVR elicited a highly statistical significant difference between the two subgroups with higher mean value in group Ia than in group Ib ($1.77\times10^6\pm1.0638\times10^6$ versus $0.08\times10^6\pm0.02282\times10^6$, $P<0.001$; Table 3).

Also, there was a positive correlation between HOMA-IR score and degree of liver fibrosis; higher HOMA-IR is significantly associated with higher stages of liver fibrosis ($r=0.542$, $P<0.05$).

Comparison between patients achieving RVR versus those with negative RVR as regard different pretreatment variables revealed a highly statistical significance regarding ALT and HOMA-IR scores ($P<0.001$) and borderline significance regarding body mass index (BMI; $P=0.08$). However, there was no statistical significance regarding age and baseline PCR levels ($P>0.05$).

Weak positive correlation between BMI and HOMA-IR scores >2.5 was encountered in group I patients, Overweight CHC patients are associated with higher HOMA-IR scores ($r=0.21$; Fig. 2).

Discussion

Sustained virological response (SVR) is defined as continued undetectable HCV RNA 24 weeks after finishing therapy. It ranges from less than 50 % to over 60 % of patients treated for chronic HCV infection genotype 4. SVR rates for HCV-4 are generally reported to be similar to or slightly higher than those for genotype 1, but lower than those for genotypes 2 and 3(Moucari et al. 2008; Poustchi et al. 2008).

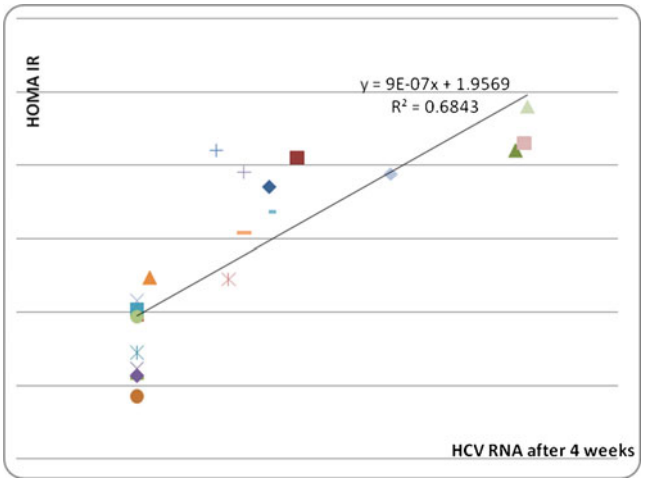

Fig. 1 Shows strong positive correlation between HOMA-IR and RVR in group Ia patients with IR >2.5 ($r=0.8272$)

Achievement of SVR is lowered by many variables including hepatitis C viral load, fibrosis stage, and age. An accurate early predicator of a patient's response to interferon therapy could reduce unnecessary and ineffective treatments and enhance cost effectiveness of treatment (Kawaguchi et al. 2009; Davis et al. 2003). RVR is a key element in the early identification of patients who may benefit from treatment regimens. Current standard therapy for HCV includes a combination of pegylated interferon (peg-IFN) and ribavirin with a sustained viral eradication rate of 55 %. A substantial proportion of patients still do not respond to peg-IFN/ribavirin therapy; therefore, predictive factors that help to identify potential non-responders are needed to limit drug exposure in patients unlikely to benefit from treatment (Kim et al. 2009). The therapeutic effect of peg-INF combination with ribavirin in patients with chronic HCV is dependent on the rapidity of virological response (VR). A RVR (serum HCV RNA undetectable after 4 weeks) is frequently an indication of early virological response (EVR) at 12 weeks and can predict SVR. Patients who become HCV-RNA negative after 4 weeks have the best chance of achieving a SVR (Ferenci et al. 2008; Kamal 2007).

IR was calculated by a simple mathematical model named HOMA score; it has been proven as a useful tool in the measurement of insulin sensitivity in euglycemic

Table 2 Comparison between HOMA-IR and RVR in both subgroups (Ia and 1b)

Item	Group Ia	Group Ib	P value	Significance
HOMA-IR (mean ± SD)	3.95±0.4907	1.7± 0.5713	<0.001	HS
RVR (no.; %)	18; 36 %	32; 64 %	<0.001	HS

HS: Highly significant

Table 3 Comparison between RVR in both subgroups (1a and 1b)

Item	Group Ia mean ± SD	Group Ib mean ± SD	P value	Significance
HCV RNA after 4 weeks (RVR)	1.77×10^6 ±1.0638× 10^6	0.08×10^6 ±0.2282× 10^6	<0.001	Highly significant

HS Highly significant

patients. HOMA-IR has emerged as a strong predictor of treatment success or failure in CHC patients (Jensen et al. 2006). However, little is known about its general relevance to treatment response in genotype 4 patients. Therefore, we conducted this prospective study to determine pretreatment variables that may be clinically useful as predictor of RVR. Factors predicting response are expected to be useful for tailoring antiviral regimens.

Our major finding in this study was the inverse relationship between IR and RVR that indicated rapid response to antiviral therapy with P value<0.001. This finding is compatible with the results of Romero-Gómez et al. (2005), who showed that IR, degree of fibrosis, and HCV genotype are independent predictors of response to anti-HCV therapy in Spanish patients; also, they reported that insulin sensitivity may improve in patients who achieve HCV RNA clearance, while it does not improve in non-responders. In match with our work, Moucari et al. (2008) stated that IR is a specific feature of CHC, associated with genotypes 1 and 4 and high serum HCV RNA level. Also, Mohamed et al. (2011) concluded that low HOMA-IR was significantly associated with RVR in chronic HCV patients. In addition, Khattab et al. (2010) determined that IR is a major determinant of both RVR and SVR in genotype 4 CHC patients. This is further

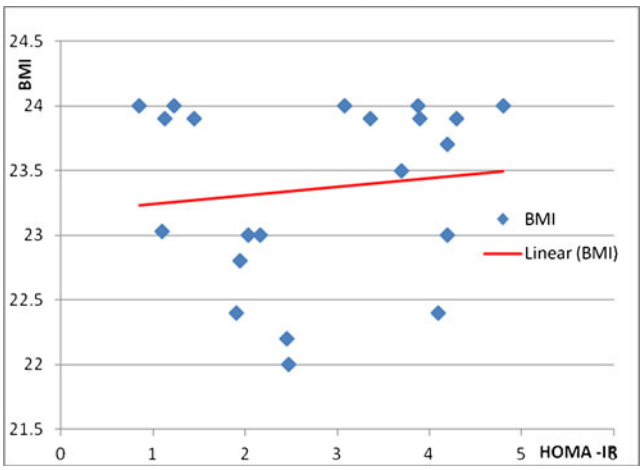

Fig. 2 Shows weak positive correlation between BMI and HOMA-IR in group Ia patients with IR >2.5 (r=0.12)

matching the opinion of Hsu et al. (2008) who concluded that high hepatitis C viral load is associated with IR in patients with CHC. In addition, Deltenre et al. (2011) concluded that IR was associated with SVR to (PEG-IFN)/ribavirin therapy for CHC, especially among difficult to treat patients. HOMA-IR would seem to be a useful tool for predicting the response to therapy. It was difficult to prove the association between the severity of IR and HCV RNA levels. Many authors suggested some theories to explain this relationship as hyperinsulinism could block in part the antiviral activity of interferon; HCV replication directly increases IR, or whether hyperinsulinemia stimulates viral replication. Furthermore, an improved glucose tolerance has been reported to follow successful antiviral treatment (Harrison 2006; Sanyal et al. 2004).

The main drawback of IR in CHC is the ability to promote fibrosis progression. Our study showed that higher HOMA-IR scores were closely associated with more severe stages of hepatic fibrosis in patients with HCV infection. This in accordance with Veldt et al. (2009), who reported that IR is a risk factor for rapid progression of hepatic fibrosis in patients that have received a liver transplantation for HCV-related liver cirrhosis. Hui et al. (2003) also reported that HCV-infected patients with stage 0 or 1 hepatic fibrosis had higher levels of HOMA scores compared with healthy volunteers matched by sex, body mass index (BMI), and waist-to-hip ratio, this work proved that HCV may induce IR at the early stage of liver disease, and provided some evidence that this effect may be driven by genotype-specific sequences. In addition, Muzzi et al. (2005) confirmed this finding by further reporting that IR is associated with liver fibrosis in non-diabetic CHC patients. This could be explained by direct effect of IR on hepatic stellate cells (HSCs) and its ability to increase connective tissue growth factor which causes production of extracellular matrix (Paradis et al. 2001). Alternatively, IR-induced hepatic lipid accumulation may increase oxidative stress, resulting in progression of hepatic fibrosis (Negro and Sanyal 2009).

In this study, pretreatment ALT is also a predictor of response to interferon and ribavirin-based therapy in which lower pretreatment ALT associated with better response (P< 0.001), this was opposed by Yu et al. (2007) whose study encompassed genotypes from 1 to 4; among patients who achieved RVR, the rate of SVR was high across all genotypes and ranged from 88 to 100 %. Baseline factors predictive of RVR included genotype, younger age, lower initial viral load, higher ALT/AST ratio, and absence of advanced fibrosis.

As regarding pretreatment viral load, our result revealed that it is not a predictor of RVR (P=0.20). On the other hand Jensen et al. (2006) reported that patients with low baseline HCV viremia (less than 600,000 IU/mL) and/or HCV infection with subtype 1b were more likely to achieve RVR than

those with baseline HCV viremia higher than 600,000 IU/mL or HCV infection with genotype 1a. In a more recent prospective trial, Ferenci et al. (2008) reported that younger age, lower body weight, genotype 4 and low baseline HCV-RNA (≤400,000 IU/ml) were significantly associated with RVR. Their study included patients with HCV genotype 1 or 4 infection treated with peg interferon alpha and ribavirin.

Comparison between patients achieving RVR versus those with negative RVR revealed borderline significance regarding BMI (P=0.08). Furthermore, weak positive correlation between BMI and HOMA-IR scores >2.5 was encountered in group I patients. Overweight CHC patients are associated with higher HOMA-IR scores (r=−0.21). This was in agreement with Tarantino et al. (2006), who demonstrated that a low-caloric diet for 3 months before initiating antiviral therapy in patients with genotype 1 CHC resulted in a significant improvement in IR as well as a 60 % end-of-treatment response rate in the low-caloric diet group as compared to the control group (17.6 %).

Conclusion

HOMA-IR was significantly associated with high RVR, progressive fibrosis stages, high pretreatment ALT levels and BMI. Our data suggests that IR is strongly affects VR. HOMA-IR would appear to be useful in predicting RVR; a decrease in IR may induce a reduction in viral load so IR should be evaluated at baseline in all chronic HCV patients before initiating interferon therapy to reduce unnecessary and ineffective treatments and enhance cost effectiveness of treatment.

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References

Davis GL, Wong JB, McHutchison JG et al (2003) Early virological response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. Hepatology 38:645–652

Deltenre P, Louvet A, Lemoine M et al (2011) Impact of insulin resistance on sustained response in HCV patients treated with pegylated interferon and ribavirin: a meta-analysis. J Hepatol 55 (6):1187–1194

Ferenci P, Laferl H, Scherzer TM et al (2008) Peginterferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virological response. Gastroenterology 135:451–458

Harrison SA (2006) Correlation between insulin resistance and hepatitis C viral load. Hepatology 43:1168

Holstein A, Hize S, Thiessen E et al (2002) Clinical implications of hepatogenous diabetes in liver cirrhosis. J Gastroenterol Hepatol 17:677–681

Hsu CS, Liu CJ, Liu CH et al (2008) High hepatitis C viral load is associated with insulin resistance in patients with chronic hepatitis C. Liver Int 28:271–277

Hui JM, Sud A, Farrell GC et al (2003) Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression. Gastroenterology 125:1695–1704

Hung HC, Wang JH, Hu TH et al (2010) Insulin resistance is associated with hepatocellular carcinoma in chronic hepatitis C infection. World J Gastroenterol 16:2265–2271

Jensen DM, Morgan TR, Marcellin P et al (2006) Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. Hepatology 43:954–960

Kamal SM, El Kamary SS, Shardell MD et al (2007) Pegylated interferon alpha-2b plus ribavirin in patients with genotype 4 chronic hepatitis C: the role of rapid and early virologic response. Hepatology 46:1732–1740

Kawaguchi T, Sata M (2010) Importance of hepatitis C virus-associated insulin resistance: therapeutic strategies for insulin sensitization. World J Gastroenterol 16:1943–1952

Kawaguchi T, Nagao Y, Tanaka K et al (2005) Causal relationship between hepatitis C virus core and the development of type 2 diabetes mellitus in a hepatitis C virus hyperendemic area: a pilot study. Int J Mol Med 16:109–114

Kawaguchi Y, Mizuta T, Oza N et al (2009) Eradication of hepatitis C virus by interferon improves whole-body insulin resistance and hyperinsulinaemia in patients with chronic hepatitis C. Liver Int 29:871–877

Khattab M, Eslam M, Sharwae MA et al (2010) Insulin resistance predicts rapid virologic response to peginterferon/ribavirin combination therapy in hepatitis C genotype 4 patients. Am J Gastroenterol 105(9):1970–1977

Kim HJ, Park JH, Park DI et al (2009) Clearance of HCV by combination therapy of pegylated interferon α-2a and ribavirin improves insulin resistance. Gut Liver 3:108–115

Kobashi-Margáin RA, Gutiérrez-Grobe Y, Uribe M et al (2010) Prevalence of type 2 diabetes mellitus and chronic liver disease: a retrospective study of the association of two increasingly common diseases in Mexico. Ann Hepatol 9:282–288

Lauer GM, Walker BD (2001) Hepatitis C virus infection. N Engl J Med 345:41–52

Maeno T, Okumura A, Ishikawa T et al (2003) Mechanisms of increased insulin resistance in non-cirrhotic patients with chronic hepatitis C virus infection. J Gastroenterol Hepatol 18:1358–1363

Matthews DR, Hosker JP, Rudenski AS et al (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419

Méndez-Sánchez N, Chávez-Tapia NC, Zamora-Valdés D et al (2007) Hepatobiliary diseases and insulin resistance. Curr Med Chem 14:1988–1999

Mohamed AA, Loutfy SA, Craik JD et al (2011) Chronic hepatitis c genotype-4 infection: role of insulin resistance in hepatocellular carcinoma. Virol J 8:496

Moucari R, Asselah T, Cazals-Hatem D (2008) Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. Gastroenterol 134(2):416–423

Muzzi A, Leandro G, Rubbia-Brandt L et al (2005) Insulin resistance is associated with liver fibrosis in non-diabetic chronic hepatitis C patients. J Hepatol 42:41–46

Negro F, Sanyal AJ (2009) Hepatitis C virus, steatosis and lipid abnormalities: clinical and pathogenic data. Liver Int 29(2):26–37

Paradis V, Perlemuter G, Bonvoust F et al (2001) High glucose and hyperinsulinemia stimulate connective tissue growth factor expression: a potential mechanism involved in progression to fibrosis in nonalcoholic steatohepatitis. Hepatology 34:738–744

Poustchi H, Negro F, Hui J et al (2008) Insulin resistance and response to therapy in patients infected with chronic hepatitis C virus genotypes 2 and 3. J Hepatol 48:28–34

Romero-Gómez M, Del Mar Viloria M, Andrade RJ et al (2005) Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. Gastroenterology 128:636–641

Sanyal AJ, Chand N, Comar K et al (2004) Hyperinsulinemia blocks the inhibition of hepatitis C virus (HCV) replication by interferon: a potential mechanism for failure of interferon therapy in subjects with HCV and nonalcoholic fatty liver disease. Hepatology 40:179A

Shintani Y, Fujie H, Miyoshi H et al (2004) Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. Gastroenterology 126:840–848

Tarantino G, Conca P, Sorrentino P et al (2006) Metabolic factors involved in the therapeutic response of patients with hepatitis C virus-related chronic hepatitis. J Gastroenterol Hepatol 21 (8):1266–1268

Veldt BJ, Poterucha JJ, Watt KD et al (2009) Insulin resistance, serum adipokines and risk of fibrosis progression in patients transplanted for hepatitis C. Am J Transplant 9:1406–1413

Yu JW, Wang GQ, Sun LJ et al (2007) Predictive value of rapid virological response and early virological response on sustained virological response in HCV patients treated with pegylated interferon alpha-2a and ribavirin. J Gastroenterol Hepatol 22:832–836

Zein NN, Abdulkarim AS, Wiesner RH et al (2000) Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol or cholestatic disease. J Hepatol 32:209–217

Zekri AR, Bahnassy AA, Abdel-Wahab SA et al (2009) Expression of pro- and anti-inflammatory cytokines in relation to apoptotic genes in Egyptian liver disease patients associated with HCV-genotype-4. J Gastroenterol Hepatol 24:416–428