Original Article

The Effects of Direct Acting Antiviral-based Therapy on Insulin Resistance Index and Metabolic Parameters in Patients with Chronic Hepatitis C

Kobkarn Ngamsrisopol, MD[1], Supatsri Sethasine, MD[1]

[1] Division of Gastroenterology and Hepatology, Department of Medicine, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

Background: Insulin resistance (IR) is a condition associated with chronic hepatitis C (CHC). The change in IR after direct antivirals (DAA)-based therapy has been interesting.

Objective: To assess the impact of DAA-based therapy on the homeostatic model assessment for insulin resistance (HOMA-IR) index and other metabolic parameters in CHC patients.

Materials and Methods: A total of 54 CHC patients with stage 2 liver fibrosis or more were enrolled. Patients with diabetes, obesity, decompensated liver disease, and HIV were excluded. HOMA-IR was calculated before onset and at end of treatment (EOT), as well as 3 months and 6 months after treatment. IR was defined as HOMA-IR greater than 2. Patients were treated according to genotype from the government policy and Thailand Practice Guideline.

Results: The mean age of patients was 53 years. Most of the patients, 40 (73.1%), were in advanced stage liver fibrosis. More than half (55.6%) had cirrhosis. More than one-third (38.8%) were overweight. Median HOMA-IR was 4.05 (0.26 to 26.22) and one-third of the patients had quantitative hepatic fat of more than 33%. There were no changes in fasting plasma glucose, insulin levels, body weight or HOMA-IR after DAA treatment in all three follow-up periods (p = 0.47, 0.48, 0.15, 0.53) respectively. Whereas a decline in the mean percentage of HOMA-IR index was seen in patients who had baseline IR, the opposite results had occurred in patients without IR at EOT and 6 months after DAA-based therapy (-25.4% vs. 356.4%, p = 0.003; -17.7% vs. 139.3%, p = 0.018). Improvement of inflammation (ALT 113 to 58 IU/L, p<0.001) and fibrosis regression were achieved at EOT (21.3 to 15.9 kPa, p<0.0001).

Conclusion: DAA-based therapy ameliorates IR in non-diabetic CHC patients with high baseline of HOMA-IR index independent of weight reduction.

Keywords: Alanine aminotransferase, Chronic hepatitis C, HOMA-IR, Insulin resistance

J Med Assoc Thai 2020;103(Suppl.8): S73-81
Website: http://www.jmatonline.com

Hepatitis C virus (HCV) infection is an important cause of chronic hepatitis C (CHC), cirrhosis and hepatocellular carcinoma. The prevalence rate is about 3% or 180 million people in the world[1]. The prevalence was about 0.5 to 2% in Thailand due to a decline of intravenous drug users and improved health check-up programs. Most patients are asymptomatic. There are many data about the relationship of CHC patients with atherosclerosis, insulin resistance, diabetes and metabolic syndrome[2].

Insulin resistance (IR) is a condition in which cells cannot use insulin effectively[3]. It is the major mechanism for the development of type 2 diabetes and a risk factor for atherosclerosis, obesity, and metabolic syndrome. There are many ways to measure insulin resistance[4]. The simplest and most convenient way of IR measurement status is the homeostasis model assessment for insulin resistance (HOMA-IR)[5]. HOMA is a calculated formula from fasting plasma glucose levels (FPG) and insulin levels. Calculated HOMA-IR correlates with the gold standard method by evaluating the insulin function from the Euglycemic hyperglycemic clamp technique. HOMA-IR was calculated from the formula: HOMA-IR = fasting insulin (mU/L) x fasting glucose (mg/dL)/405.

CHC patients have associated insulin resistance, liver steatosis and metabolic syndrome by demonstrating an increase in HOMA-IR, FPG and fasting serum insulin levels as compared to the general population[6-13]. Previous studies reported the incidence of insulin resistance in CHC patients in the range of 32 to 78%[6-9] using a cut point HOMA-IR

Correspondence to:

Sethasine S.

Division of Gastroenterology and Hepatology, Department of Medicine, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok 10300, Thailand.

Phone: +66-2-2443480

Email: supatsri9@hotmail.com, supatsri@nmu.ac.th

How to cite this article:

Ngamsrisopol K, Sethasine S. The Effects of Direct Acting Antiviral-based Therapy on Insulin Resistance Index and Metabolic Parameters in Patients with Chronic Hepatitis C. J Med Assoc Thai 2020;103(Suppl.8): S73-81.

doi.org/10.35755/jmedassocthai.2020.S08.12002

from 1.5 to >4[8,10,11].

There were previous data regarding CHC patients who had achieved sustained virological response (SVR) with pegylated interferon and ribavirin therapy associated with a decrease in HOMA-IR, as compared to no change in HOMA-IR in those without SVR. Moreover, in those patients who had not achieved SVR, an increased HOMA-IR by 6 to 12 months of follow-up was found[12-14]. A cut point value of HOMA-IR <2 is 6.5 times more likely to result in SVR[15], however, some studies show an unclear relationship between HOMA-IR and SVR[16]. Meta-analysis have shown that insulin resistance is not associated with genotype of CHC[17,18].

In the era of direct acting antiviral (DAA) treatment, studies have shown a significant reduction in HOMA-IR in CHC patients who had achieved SVR with DAA-based therapy[19,20]. Currently DAA regimens are eligible in Thailand. The aim of this research is to study the relationship between CHC patients who have been treated with DAA regimens and their associated change in insulin resistance.

Materials and Methods

Study design and study population

A total of 54 CHC participants were treated in the outpatient liver clinic department of Vajira Hospital. They were enrolled to this prospective cohort study (COA170/2561) from December 2018 to November 2019. Selection criteria were according to Thailand's treatment guideline 2016 which was eligible to patients age 18 to 70 years, HCV viral load ≥5,000 IU/ml and significant liver fibrosis with a value of greater than or equal to 7 kilopascal (kPa) (≥F2) by transient elastography (TE) measurement within 12 months. Cirrhosis in this study was documented by ultrasonography or transient elastography ≥13 kPa with Child-Pugh score ≤9 and MELD score ≤18. Enrolled patients were required to quit drinking alcohol 6 months prior to the onset of the study, not be terminally ill or have an uncontrolled underlying disease, active malignancy, pregnancy, refrain from contraception use and have renal function with eGFR ≥30 ml/min. Prospective subjects with diabetes, metabolic syndrome, morbid obesity (BMI ≥30 kg/m^2), co-infection with HIV or HBV were excluded. Selected patients were given the information regarding CHC disease and had provided informed consent before treatment according to Thailand access policy to DAA policy. Demographic data, underlying disease, body weight and body mass index (BMI) were recorded. Thai BMI was categorized by normal (18.5 to 22.9 kg/m^2), overweight (23 to 24.9 kg/m^2), and obesity (25 to 29 kg/m^2). HCV viral loads were collected at baseline and 12 weeks after end of treatment to assess SVR. Venous blood sample were measured to determine fasting plasma glucose, insulin, HbA1c, C-peptide, total cholesterol (TC), LDL-C, triglyceride, alanine aminotransferase (ALT) and alpha-fetoprotein (AFP) after fasting at least 8 hours to assess metabolic factors, before and at end of treatment (EOT), as well as 3 months and 6 months after EOT. The insulin resistance index used HOMA-IR method which was calculated from fasting insulin (mU/L) x fasting glucose (mg/dL)/405. Liver stiffness was measured by transient elastography (Fibroscan) at baseline, EOT, as well as 3 months and 6 months after EOT. Controlled attenuation parameter (CAP) was utilized to defined severity of hepatic steatosis. Grading of steatosis was defined as less than 10% of hepatic steatosis; S0 (<215), 11 to 33% of hepatic steatosis; S1 (216 to 252), 34 to 66% of hepatic steatosis; S2 (253 to 296) and >67% of hepatic steatosis; S3 (>296). Grading of fibrosis was defined as, F2; significant fibrosis (7 to 9), F3; advanced fibrosis (9 to 13) and F4; advanced fibrosis/cirrhosis (>13).

Patients who met inclusion criteria were prescribed selected DAA based regimens according to genotype. Sofosbuvir and ledipasvir were used for non-cirrhotic genotypes 1 and 6 and ribavirin was added if cirrhosis was diagnosed. Sofosbuvir, pegylated interferon and ribavirin were used for genotype 3 irrespective of cirrhosis. All patients received a total of 12 weeks of treatment. HCV viral load was evaluated at 12 weeks after EOT for SVR.

Statistical analysis

Descriptive data were expressed as percentile and comparative data were expressed as mean (standard deviation), a mean comparison of the difference in HOMA-IR values between baseline and three periods after EOT. Changes in mean scores over three time point of insulin resistance and other metabolic parameters were evaluated by repeated measures ANOVA. The percentage change of HOMA-IR score were reported by error line chart. Data were analyzed by SPSS 16.0 and *p*-value <0.05 level was assumed as significant.

Results

Table 1 shows baseline characteristics of patients at study inclusion. A total of 54 patients completed 3 months of treatment, and 48 subjects received 6 months of follow-up after EOT. The mean age was 53 years and 59% those were male. Thirty out of 54 (55.5%) had cirrhosis and most of the patients 40 (73.1%) were in advanced stage of liver fibrosis. Nearly one-third (31.5%) had underlying diseases, consisting of hyperlipidemia in 4 (7.4%), fatty liver disease in 5 (9.2%) and other chronic diseases in 8 (14.8%). Twenty-four patients were genotype 1 (44.4%), the others were genotype 3 and 6 (38.8% and 16.7% respectively). The mean viral load was 5.9±1.0 log IU/mL, mean weight was 64.7±13.7 kg, BMI was within the normal range 23.9±3.5 kg /m^2; 21 of the patients (38.8%) were overweight. Baseline mean FPG was 97.9±10.2 mg/dl; 20 patients (37%) had impaired FPG. Median HOMA-IR was 4.05 (0.26 to 26.22) which was relatively high for insulin resistance. Other mean metabolic parameters were: C-peptide 3.1±1.6 ng/ml, HbA1C 5.7±1.1%, LDL 111.9±35 mg/dl, TG 106.2±53 mg/dl and TC 184.6±49.6 mg/dl. The mean ALT was 113.4±73 U/L, and the median liver stiffness was 16.9 (7.4 to 75) kPa. Mean liver steatosis (CAP) was 231.3±53.4 dB /m, in half of which there was less than 10% of hepatic fatty change (S0).

Table 1. Baseline characteristics of 54 chronic hepatitis C patients

Parameters	Results
Age (years)	53.0 (8.9)
Male; n (%)	32 (59.2)
Underlying disease; n (%)	17 (31.5)
Dyslipidemia	4 (7.4)
Fatty liver	5 (9.2)
Cirrhosis, n (%)	31 (57.4)
HCV viral load (log)	5.9 (1.0)
Hepatitis C genotype, n (%)	
1	24 (44.4)
3	21 (38.8)
6	9 (16.7)
Body mass index (kg/m^2)	23.9 (3.5)
Normal (18.5 to 24.9), n (%)	33 (61.1)
Overweight (25 to 29.9), n (%)	21 (38.8)
Body weight (kg)	64.7 (13.7)
Fasting plasma glucose (mg/dl)	97.9 (10.2)
Impair fasting glucose (mg/dl), n (%)	20 (37)
Insulin level (uIU/ml)	19.8 (17.4)
HOMA-IR	4.05 (0.26 to 26.22)*
C-peptide (ng/ml)	3.1 (1.6)
Hemoglobin A1c (%)	5.7 (1.1)
Alanine aminotransferase (U/L)	113.4 (73.2)
LDL-C (mg/dl)	111.9 (35.0)
Triglyceride (mg/dl)	106.2 (53)
Total cholesterol (mg/dl)	184.6 (49.6)
Alpha-fetoprotein (IU/ml)	5.5 (1.49 to 137)*
CAP score (dB/m)	231.3 (53.4)
Grading of CAP score (liver steatosis), n (%)	
0	27 (50)
1	9 (16.7)
2	12 (22.2)
3	6 (11.1)
Liver stiffness (kPa)	16.9 (7.4 to 75)*
Grading of fibrosis, n (%)	
1	1 (1.9)
2	13 (24.1)
3	10 (18.5)
4	30 (55.6)

Data are expressed as mean (SD) unless specified.
* Data are presented in median (range)

Mean liver steatosis in the others were S1, S2 and S3 in 9 (16.7%), 12 (22.2%) and 6 (11.1%) respectively.

Change of insulin resistance, other metabolic parameters across the study period

The protocol followed metabolic changes before and after EOT period. The result showed that there were no change in FBS, insulin levels, mean BW and HOMA-IR after all three FU periods. HbA1c was decreased significantly over three time point (p<0.001) (Table 2).

Change of metabolic parameter along with HCV genotype

Twenty-one patients were in genotype 3 (G3), and 33 (61.1%) were non-genotype 3 (non-G3). It was consistently found that HOMA-IR and insulin levels did not change at EOT, nor after 3 and 6 months in both genotype subgroups. Although FPG was statistically reduced in the G3 group for all 3 periods (p = 0.03), body weight was regained significantly within 6 months after therapy (p = 0.002). A trend of FPG decline was not seen in the non-G3 group. Declination of HbA1c were observed in both groups only at EOT (Table 3).

Insulin resistance was defined as HOMA-IR ≥2. We categorized the HOMA-IR by using the cut-off value of 2. Thirteen participants (24%) were in the subgroup of HOMA-IR <2 and 41 (76%) in the subgroup of HOMA-IR ≥2. The latter group experienced a significant decrease in mean percentage change of HOMA-IR score as compared with an increase in mean percentage change of HOMA-IR score in the former group at EOT and 6 months after EOT (-25.44% vs. 356.4%; p = 0.003); (-17.7% vs. 139.3%; p = 0.018) (Figure 1).

Change of lipid profile after DAA-based treatment

Total cholesterol (TC), LDL, but not triglyceride, statistically increased significantly at 3 months and 6 months after EOT (Table 2). An increase in TC and LDL level at 3 and 6 months after EOT was seen irrespective of cirrhosis (Table 4).

Change of fibrosis after DAA-based treatment

A statistically significant reduction in liver necroinflammation, represented by the ALT together with liver stiffness, was shown at EOT, as well as 3 and 6 months after EOT. More than half of the patients, 26 (54.2%), had benefited from fibrotic stage regression. Even in advanced stage,16 of 40 (40%) of patients had received this benefit. Interestingly, nearly half of these sixteen patients, 7 (43.8%), in advanced stage achieved fibrotic regression to significant fibrotic stage, particularly 2 of them had more than one stage of fibrotic regression. We observed that the reduction of mean percentage of liver stiffness in those with cirrhosis was greater than in the non-cirrhosis group, however it was not statistically significant by 6 months of FU (-23.9% vs. -16.8%; p = 0.23) (Table 5, Figure 2).

Discussion

Forty-eight of 54 patients (88.8%) had completed 6 months of follow-up. Due to the exclusion of prospective

Table 2. Mean of metabolic parameters across study periods

Metabolic parameters	Mean (SD)	*p*-value
FBS (mg/dl)		
Before treatment	97.9 (10.2)	0.477
EOT	96.5 (11.6)	
3 months EOT	99.4 (18.2)	
6 months EOT	98.7 (14.5)	
Insulin level (uIU/ml)		
Before treatment	19.8 (17.4)	0.485
EOT	16.2 (12.8)	
3 months EOT	19.1 (26.4)	
6 months EOT	17.3 (25.3)	
HOMA-IR		
Before treatment	4.9 (4.6)	0.529
EOT	3.9 (3.2)	
3 months EOT	5.3 (10.8)	
6 months EOT	4.3 (6.4)	
C-peptide (ng/ml)		
Before treatment	3.1 (1.6)	0.662
EOT	2.9 (1.5)	
3 months EOT	3.0 (2.1)	
6 months EOT	2.9 (1.9)	
HemoglobinA1c (%)		
Before treatment	5.7 (1.1)	<0.001*
EOT	5.3 (1.0)	
3 months EOT	5.7 (0.9)	
6 months EOT	5.6 (0.7)	
Body weight (Kg)		
Before treatment	64.7 (13.7)	0.156
EOT	64.2 (14.1)	
3 months EOT	65.0 (13.9)	
6 months EOT	64.6 (14.2)	
Alanine aminotransferase (U/L)		
Before treatnment	113.4 (73.2)	<0.001*
EOT	58.2 (44.1)	
3 months EOT	39.9 (23.1)	
6 months EOT	33.7 (18.2)	
LDL- C (mg/dl)		
Before treatment	111.9 (35.0)	<0.001*
EOT	118.9 (41.6)	
3 months EOT	133.1 (41.8)	
6 months EOT	129.8 (42.9)	
Triglyceride (mg/dl)		
Before treatment	106.2 (53.0)	0.408
EOT	109.2 (53.2)	
3 months EOT	100.0 (50.5)	
6 months EOT	100.4 (57.2)	
Total cholesterol (mg/dl)		
Before treatment	184.6 (49.6)	<0.001*
EOT	192.7 (54.1)	
3 months EOT	212.1 (53.4)	
6 months EOT	206.8 (55.9)	
Alpha-fetoprotein (IU/ml)		
Before treatment	12.3 (21.6)	0.023*
6 months EOT	6.4 (5.5)	
CAP score (dB/m)		
Before treatment	231.3 (53.4)	0.023*
EOT	247.3 (44.5)	
3 months EOT	231.9 (43.0)	
6 months EOT	223.8 (49.9)	
Liver stiffness (kPa)		
Before treatment	21.3 (15.6)	<0.001*
EOT	15.9 (11.7)	
3 months EOT	15.7 (12.7)	
6 months EOT	13.3 (9.0)	

EOT = end of treatment

participants with obesity, nearly two-thirds of patients had a mean BMI within the normal range. According to health systems policy, some patients were not eligible to participate and deferred treatment, thus most of our patients were in advanced stage liver fibrosis when initiate reimbursement. Some studies demonstrated that HCV infection caused down-regulation of insulin receptor substrate and interfered with signaling transduction[21,22]. The previous prevalence of IR was approximately one-fourth of CHC patients[23] although prevalence increased to 50% when associated with other co-metabolic diseases[19].

The presence of IR is associated with liver disease progression. Our mean HOMA-IR was high due to more than half of the patients having cirrhosis as supported by two previous studies which showed that a higher score correlated with severity of liver disease[24,25]. Donadon et al reported the mean levels of HOMA-IR in cirrhosis was twofold as compared with the level in CHC (5.4 vs. 2.7)[24]. HOMA-IR of ≥2, representing a higher HOMA-IR in advance fibrosis when compared with the level in low fibrosis, it was not significantly different (5.2 vs. 4.3; $p = 0.55$) in our study. Overweight and/or significant liver steatosis was found in more than one-third of patients which may be another reason for the explanation of high mean HOMA-IR in this study.

Table 3. Change of body weight, glucose parameter and liver steatosis according to genotype

Metabolic parameters, mean (SD)	Genotype 3	*p*-value	Non-genotype 3	*p*-value
Body weight (kg)				
Before treatment	64.1 (16.2)	0.002*	65.0 (12.1)	0.320
EOT	63.7 (16.3)		64.4 (12.7)	
3 months EOT	64.9 (16.6)		65.0 (12.8)	
6 months EOT	66.9 (16.9)		63.2 (12.2)	
HOMA-IR				
Before treatment	5.5 (5.8)	0.428	4.6 (3.8)	0.399
EOT	4.8 (4.1)		3.4 (2.3)	
3 months EOT	4.1 (2.8)		6.0 (13.6)	
6 months EOT	5.9 (9.8)		3.3 (2.3)	
Hemoglobin A1C (%)				
Before treatment	5.9 (1.7)	0.304	5.5 (0.5)	<0.001
EOT	5.6 (1.8)		5.1 (0.8)	
3 months EOT	5.7 (1.1)		5.7 (0.7)	
6 months EOT	5.7 (0.8)		5.6 (0.6)	
Fasting plasma glucose (mg/dl)				
Before treatment	99.5 (10.1)	0.030	96.9 (10.2)	0.058
EOT	94.4 (10.2)		97.8 (12.4)	
3 months EOT	92.4 (11.6)		103.8 (20.3)	
6 months EOT	97.6 (10.2)		99.4 (16.9)	
Insulin level (uIU /ml)				
Before treatment	21.6 (20.6)	0.770	18.7 (15.1)	0.342
EOT	20.1 (16.6)		13.8 (9.1)	
3 months EOT	18.6 (15.1)		19.3 (31.8)	
CAP score (dB/m)				
Before treatment	253.1 (54.9)	0.012	217.4 (48.2)	0.011
EOT	247.3 (44.9)		247.3 (45)	
3 months EOT	225.4 (49.4)		236 (38.7)	
6 months EOT	231.9 (50.7)		218.4 (49.5)	

Even after highly successful DAA based therapy, FPG, insulin levels and HOMA-IR did not have any statistically significant changes in all of follow-up periods. Three-month periods of peginterferon plus DAA regimens treatment in genotype 3 patients caused some anorexia and fatigue which resulted in a reduction in FPG and HbA1c at end of treatment.

In the era of pegylated interferon plus Ribavirin therapy, SVR was associated with significant reduction of IR in many studies[10,12,13]. Some studies showed HOMA-IR ≥2 was associated with SVR achievement in genotype 1 patients[11,12] but in meta-analysis it was shown that interferon-treated patients with baseline IR associated with lower SVR regardless of genotype[17,18,26]. DAA therapy has conflicting results regarding changes of HOMA-IR due to different ethnic groups and heterogeneity of HOMA-IR cut point[27]. Previous studies by Doyle et al[28] and Meissner et al[29] reported no changes in HOMA-IR in non-diabetes CHC genotype 1 patients whom achieved SVR with interferon free regimens.Another study from Elhelbawy et al showed IR improves significantly in SVR patients including CHC patients with diabetes[20].

We observed a fluctuation of HOMA-IR after treatment regardless of HCV genotype. There is a study showing no relationship between HOMA-IR and any specific HCV-genotype or viral load[24,30]. From a previous study populated by Thai CHC patients and meta-analysis, insulin resistance (IR) was defined as HOMA-IR ≥2. We used this cut point to divide our groups into low HOMA-IR score (<2) and high HOMA-IR score (≥2)[31]. Most of our patients (76%) were in a status of pretreatment IR. For DAA-based regimen in our study, all patients achieved SVR. Although the median HOMA-IR score did not significantly change, a significant decrease in mean percentage change of HOMA-IR was observed in the high IR group. We demonstrated

the improvement of insulin resistance in patients with high IR status implicates clinical benefits of viral eradication irrespective of genotype. Weight loss after interferon-based therapy was a confounding factor for a decline of IR[14]. Our study showed after therapy a declination in percentage of HOMA-IR in IR group was independent of body weight as no significant reduction was observed after treatment even in genotype 3 patients.

HCV infection associated with increasing accumulation of fatty acids in hepatocytes by increasing fatty acid synthesis levels. HCV interfere lipid metabolism by the compacted virion with lipoproteins termed lipoviral particles causing enhanced lipid droplet accumulation in hepatocytes and decreased secretion of VLDL[32,33]. Our study showed that after viral eradication cause increase the TC and LDL-C after all of follow-up periods. These effects were observed in every stage of liver fibrosis. Previous studies supported the effect of an increase of TC and LDL after DAA regimens seen in CHC genotype 1 with SVR[20,34-36]. We reported a significant reduction of quantitative steatosis seen only in genotype 3 after treatment. As supported by that mechanism of hepatic steatosis in genotype 3 is a direct effect of core proteins which interfere with the expression of peroxisome proliferators-activated receptor (PPAR)-α resulting in decreased VLDL secretion[37]. Regression of hepatic steatosis was also observed in the genotype 3 patients who had achieved SVR by interferon-based therapy[38].

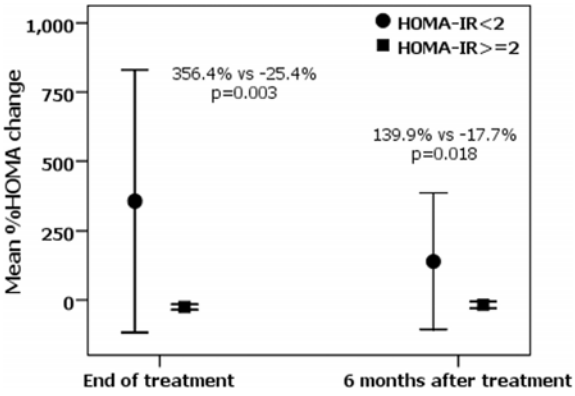

Figure 1. Percentage change of HOMA-IR score between HOMA-IR subgroup after DAA-based therapy.

Not only improvement of necroinflammation but also decreases in liver stiffness were shown at EOT. Liver stiffness decreased by 25.6% at EOT (21.3 vs. 15.9 kPa, $p<0.0001$), together with improvement of liver inflammation (ALT 113 vs. 58 IU/L, $p<0.001$). An initial rapid decline of liver stiffness may be influenced by a reduction in liver inflammation. After resolution of necroinflammation, a further decrement of liver stiffness by 6 months follow-up occurred. A dynamic of fibrosis regression was shown by an additional 12% of liver stiffness decrement from value at EOT to value at 6 months follow-up (15.9 to 13.3 kPa). The total reduction in liver stiffness was higher than 30% at 6 months of follow-up. Treatment benefited not only by reduced fibrotic stages in over half of all patients but more than one-third (40%) of advanced disease patients could achieve fibrosis regression. Moreover, some of the advanced disease patients were down staged to significant fibrosis as well. As supported from many studies, successful DAA treatment results in a benefit of initial resolution of liver inflammation and improvement in liver fibrosis[39-41].

The limitation of this study was firstly, a few of our research patients were in high HOMA-IR and non-advanced fibrotic stage, so we could not conclude whether this group would have experienced a benefit of IR improvement after SVR. Secondly, a short period of follow-

Table 4. Change in total cholesterol and LDL-C in according to stage of liver disease

Lipid parameters, mean (SD)	Cirrhosis (n = 30)	*p*-value	Non-cirrhosis (n = 24)	*p*-value
LDL-C (mg/dl)				
Before treatment	110.5 (37.9)	<0.001	113.7 (31.9)	0.007
EOT	110.6 (39.2)		129.4 (43.1)	
3 months EOT	126.5 (40.7)		141.4 (42.6)	
6 months EOT	122.3 (41.5)		139.4 (44)	
Total cholesterol (mg/dl)				
Before treatment	184.6 (51.9)	<0.001	184.6 (47.6)	0.007
EOT	183.4 (50.1)		204.4 (57.7)	
3 months EOT	207.7 (54.2)		217.6 (53.0)	
6 months EOT	199.4 (56.1)		216.4 (55.5)	

EOT = end of treatment

up for evaluation of fibrotic regression, a period of follow-up longer than 24 weeks after EOT would be needed.

Conclusion

In high baseline of homeostasis model assessment for insulin resistance index (HOMA-IR), successful DAA-based therapy in non-obese CHC had improved insulin resistance independent of weight reduction.

What is already known on this topic?

Treating CHC patients using direct acting antiviral-based therapy can improve insulin sensitivity.

What this study adds?

Treating CHC patients, who have obtained a HOMA score greater than two, using direct acting antiviral-based therapy can ameliorate associated insulin resistance uncomplicated by weight reduction.

Table 5. Change of alanine aminotransferase and fibrotic regression after treatment

Variables	n	Mean (SD)	*p*-value
Alanine aminotransferase (U/L)			
Before treatment	54	113.4 (73.2)	<0.001
EOT	54	58.2 (44.1)	
3 months EOT	54	39.9 (23.1)	
6 months EOT	48	33.7 (18.2)	
Liver stiffness (kPa)			
Before	54	21.3 (15.6)	<0.001
End of treatment	54	15.9 (11.7)	
3 months EOT	54	15.7 (12.7)	
6 months EOT	48	13.3 (9.0)	

EOT = end of treatment

Acknowledgement

This study was supported by a grant from Navamindradhiraj University Research Fund and the Gastroenterological Association of Thailand.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Craxi A, Laffi G, Zignego AL. Hepatitis C virus (HCV) infection: a systemic disease. Mol Aspects Med 2008;29:85-95.
2. Zignego AL, Craxi A. Extrahepatic manifestations of hepatitis C virus infection. Clin Liver Dis 2008;12: 611-36.
3. Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol 2012;59:635-43.
4. Singh B, Saxena A. Surrogate markers of insulin resistance: A review. World J Diabetes 2010;1:36-47.
5. Borai A, Livingstone C, Ferns GA. The biochemical assessment of insulin resistance. Ann Clin Biochem 2007;44:324-42.
6. Moucari R, Asselah T, Cazals-Hatem D, Voitot H, Boyer N, Ripault MP, et al. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. Gastroenterology 2008;134:416-23.
7. Lonardo A, Ballestri S, Adinolfi LE, Violi E, Carulli L, Lombardini S, et al. Hepatitis C virus-infected patients are 'spared' from the metabolic syndrome but not from insulin resistance. A comparative study of nonalcoholic fatty liver disease and hepatitis C virus-related steatosis. Can J Gastroenterol 2009;23:273-8.
8. Duseja A, Dhiman RK, Chawla Y, Thumburu KK, Kumar A, Das A, et al. Insulin resistance is common in patients with predominantly genotype 3 chronic hepatitis C. Dig Dis Sci 2009;54:1778-82.

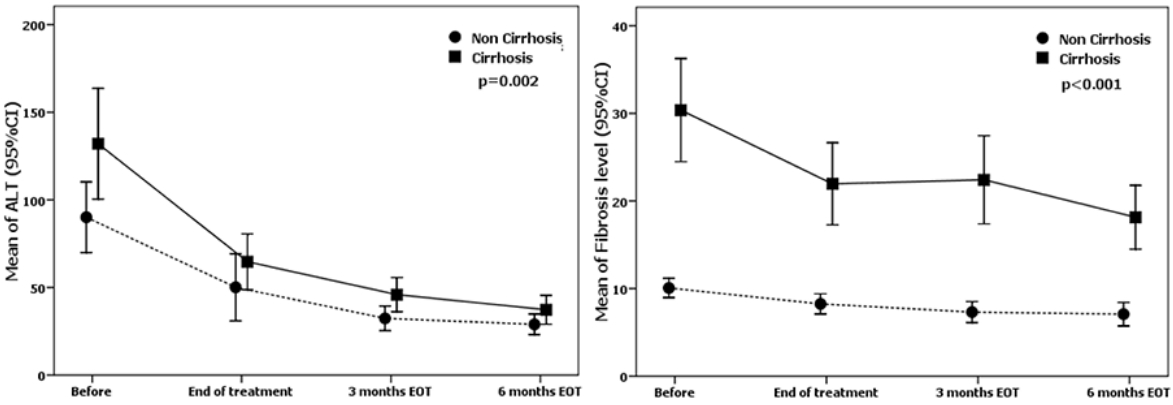

Figure 2. Change of alanine aminotransferase and fibrotic regression after treatment in chronic hepatitis C patients.

9. Peres DP, Cheinquer H, Wolf FH, Cheinquer N, Falavigna M, Peres LD. Prevalence of insulin resistance in chronic hepatitis C genotype 1 and 3 patients. Ann Hepatol 2013;12:871-5.
10. Del Campo JA, Ampuero J, Rojas L, Conde M, Rojas A, Maraver M, et al. Insulin resistance predicts sustained virological response to treatment of chronic hepatitis C independently of the IL28b rs12979860 polymorphism. Aliment Pharmacol Ther 2013;37:74-80.
11. Eslam M, Aparcero R, Mousa YI, Grande L, Shaker Y, Ali A, et al. Insulin resistance impairs viral dynamics independently of ethnicity or genotypes. J Clin Gastroenterol 2012;46:228-34.
12. Romero-Gomez M, Del Mar Viloria M, Andrade RJ, Salmeron J, Diago M, Fernandez-Rodriguez CM, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. Gastroenterology 2005;128:636-41.
13. Tseng CH, Hsu YC, Chang CY, Lin CW, Lin JT, Mo LR. Change in insulin resistance according to virological response during antiviral treatment for hepatitis C virus infection. Adv Dig Med 2016;3:43-8.
14. Conjeevaram HS, Wahed AS, Afdhal N, Howell CD, Everhart JE, Hoofnagle JH. Changes in insulin sensitivity and body weight during and after peginterferon and ribavirin therapy for hepatitis C. Gastroenterology 2011;140:469-77.
15. Poustchi H, Negro F, Hui J, Cua IH, Brandt LR, Kench JG, et al. Insulin resistance and response to therapy in patients infected with chronic hepatitis C virus genotypes 2 and 3. J Hepatol 2008;48:28-34.
16. Villar LM, Caldas GC, Scalioni LP, Miguel JC, Silva EFD, Marques VA, et al. High prevalence of insulin resistance among Brazilian chronic hepatitis C patients. Arch Endocrinol Metab 2017;61:628-32.
17. Eslam M, Aparcero R, Kawaguchi T, Del Campo JA, Sata M, Khattab MA, et al. Meta-analysis: insulin resistance and sustained virological response in hepatitis C. Aliment Pharmacol Ther 2011;34:297-305.
18. Laurito MP, Parise ER. Association between insulin resistance and sustained virologic response in hepatitis C treatment, genotypes 1 versus 2 and 3: systematic literature review and meta-analysis. Braz J Infect Dis 2013;17:555-63.
19. Adinolfi LE, Nevola R, Guerrera B, D'Alterio G, Marrone A, Giordano M, et al. Hepatitis C virus clearance by direct-acting antiviral treatments and impact on insulin resistance in chronic hepatitis C patients. J Gastroenterol Hepatol 2018;33:1379-82.
20. Elhelbawy M, Abdel-Razek W, Alsebaey A, Hashim M, Elshenawy H, Waked I. Insulin resistance does not impair response of chronic hepatitis C virus to direct-acting antivirals, and improves with the treatment. Eur J Gastroenterol Hepatol 2019;31:16-23.
21. Pazienza V, Clement S, Pugnale P, Conzelman S, Foti M, Mangia A, et al. The hepatitis C virus core protein of genotypes 3a and 1b downregulates insulin receptor substrate 1 through genotype-specific mechanisms. Hepatology 2007;45:1164-71.
22. Kawaguchi T, Yoshida T, Harada M, Hisamoto T, Nagao Y, Ide T, et al. Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. Am J Pathol 2004;165:1499-508.
23. Dai CY, Yeh ML, Huang CF, Hou CH, Hsieh MY, Huang JF, et al. Chronic hepatitis C infection is associated with insulin resistance and lipid profiles. J Gastroenterol Hepatol 2015;30:879-84.
24. Donadon V, Balbi M, Perciaccante A, Casarin P, Zanette G. Insulin resistance and hyperinsulinemia in patients with chronic liver disease and hepatocellular carcinoma. Endocrinol Diabetes 2009;2:25-33.
25. Zaghlol MS, Qasem MTA-SA, Mohamed HMM, Omar HS. Insulin resistance in non diabetic chronic hepatitis C patients. J Med Pharm Sci 2017;1:63-72.
26. Deltenre P, Louvet A, Lemoine M, Mourad A, Fartoux L, Moreno C, et al. Impact of insulin resistance on sustained response in HCV patients treated with pegylated interferon and ribavirin: a meta-analysis. J Hepatol 2011;55:1187-94.
27. Eslam M, Kawaguchi T, Del Campo JA, Sata M, Khattab MA, Romero-Gomez M. Use of HOMA-IR in hepatitis C. J Viral Hepat 2011;18:675-84.
28. Doyle MA, Galanakis C, Mulvihill E, Crawley A, Cooper CL. Hepatitis C direct acting antivirals and ribavirin modify lipid but not glucose parameters. Cells 2019;8:252.
29. Meissner EG, Lee YJ, Osinusi A, Sims Z, Qin J, Sturdevant D, et al. Effect of sofosbuvir and ribavirin treatment on peripheral and hepatic lipid metabolism in chronic hepatitis C virus, genotype 1-infected patients. Hepatology 2015;61:790-801.
30. Tsochatzis E, Manolakopoulos S, Papatheodoridis GV, Hadziyannis E, Triantos C, Zisimopoulos K, et al. Serum HCV RNA levels and HCV genotype do not affect insulin resistance in nondiabetic patients with chronic hepatitis C: a multicentre study. Aliment Pharmacol Ther 2009;30:947-54.
31. Witeerungrot T, Piratvisuth T Kanwgurn S. Prevalence of insulin resistance in Thai patients with chronic hepatitis C. Thai J Gastroenterol 2009;10:152-6.
32. Kanda T, Moriyama M. Direct-acting antiviral agents against hepatitis C virus and lipid metabolism. World J Gastroenterol 2017;23:5645-9.
33. Felmlee DJ, Hafirassou ML, Lefevre M, Baumert TF, Schuster C. Hepatitis C virus, cholesterol and lipoproteins—impact for the viral life cycle and pathogenesis of liver disease. Viruses 2013;5:1292-324.
34. Morales AL, Junga Z, Singla MB, Sjogren M, Torres D. Hepatitis C eradication with sofosbuvir leads to significant metabolic changes. World J Hepatol 2016;8:1557-63.
35. Endo D, Satoh K, Shimada N, Hokari A, Aizawa Y. Impact of interferon-free antivirus therapy on lipid

profiles in patients with chronic hepatitis C genotype 1b. World J Gastroenterol 2017;23:2355-64.
36. Gitto S, Cicero AFG, Loggi E, Giovannini M, Conti F, Grandini E, et al. Worsening of Serum Lipid Profile after Direct Acting Antiviral Treatment. Ann Hepatol 2018;17:64-75.
37. Abenavoli L, Masarone M, Peta V, Milic N, Kobyliak N, Rouabhia S, et al. Insulin resistance and liver steatosis in chronic hepatitis C infection genotype 3. World J Gastroenterol 2014;20:15233-40.
38. Castera L, Hezode C, Roudot-Thoraval F, Lonjon I, Zafrani ES, Pawlotsky JM, et al. Effect of antiviral treatment on evolution of liver steatosis in patients with chronic hepatitis C: indirect evidence of a role of hepatitis C virus genotype 3 in steatosis. Gut 2004;53:420-4.
39. Laursen TL, Siggaard CB, Kazankov K, Sandahl TD, Moller HJ, Tarp B, et al. Time-dependent improvement of liver inflammation, fibrosis and metabolic liver function after successful direct-acting antiviral therapy of chronic hepatitis C. J Viral Hepat 2020;27:28-35.
40. Knop V, Hoppe D, Welzel T, Vermehren J, Herrmann E, Vermehren A, et al. Regression of fibrosis and portal hypertension in HCV-associated cirrhosis and sustained virologic response after interferon-free antiviral therapy. J Viral Hepat 2016;23:994-1002.
41. Bachofner JA, Valli PV, Kroger A, Bergamin I, Kunzler P, Baserga A, et al. Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. Liver Int 2017;37:369-76.

ผลของยาต้านไวรัสชนิดออกฤทธิ์โดยตรงต่อการเปลี่ยนแปลงของภาวะดื้ออินซูลินและค่าเมตาบอลิกในการรักษาผู้ป่วยไวรัสตับอักเสบซีเรื้อรัง

กอบกาญจน์ งามศรีโสภณ, สุภัทศรี เศรษฐสินธุ์

ภูมิหลัง: ภาวะดื้ออินซูลินมีความสัมพันธ์กับไวรัสตับอักเสบซีเรื้อรัง ผู้นิพนธ์สนใจศึกษาการเปลี่ยนแปลงของภาวะดื้ออินซูลินต่อการรักษาไวรัสตับอักเสบซีเรื้อรังด้วยยาต้านไวรัสชนิดออกฤทธิ์โดยตรง

วัตถุประสงค์: เพื่อศึกษาการเปลี่ยนแปลงของของภาวะดื้ออินซูลินจากดัชนี homeostatic model assessment of insulin resistance (HOMA-IR) และการเปลี่ยนแปลงทางเมตาบอลิกในผู้ป่วยไวรัสตับอักเสบซีที่ได้รับการรักษาด้วยยาต้านไวรัสชนิดออกฤทธิ์โดยตรง

วัสดุและวิธีการ: ผู้เข้าร่วมศึกษา 54 คน ที่มีค่าพังผืดเนื้อตับมากกว่าหรือเท่ากับระยะ F2 ผู้ป่วยเบาหวาน อ้วน ตับแข็งระยะสุดท้าย และผู้ติดเชื้อเอชไอวีจะถูกคัดออกจากการศึกษาประเมินภาวะดื้ออินซูลินโดยวิธีคำนวนค่า HOMA-IR ก่อนการรักษา, สิ้นสุดการรักษา, หลังสิ้นสุดการรักษาที่ 3 เดือนและ 6 เดือน ค่า HOMA-IR มากกว่าเท่ากับ 2 บ่งชี้ถึงภาวะดื้ออินซูลิน การรักษาเป็นไปตามชนิดสายพันธุ์และแนวทางการรักษาไวรัสตับอักเสบซีเรื้อรังของประเทศไทย

ผลการศึกษา: ผู้เข้าร่วมศึกษามีอายุเฉลี่ย 53 ปี 40 คน (ร้อยละ 73.1) มีค่าพังผืดระยะลุกลามร้อยละ 55.6 มีภาวะตับแข็งร้อยละ 38.8 มีน้ำหนักเกินค่ามาตรฐาน, ค่ามัธยฐาน HOMA-IR เท่ากับ 4.05 (0.26 ถึง 26.22) และหนึ่งในสามของผู้ป่วยมีปริมาณไขมันสะสมในตับมากกว่าร้อยละ 33 เมื่อสิ้นสุดการรักษา ไม่พบการเปลี่ยนแปลงของค่ากลูโคสในพลาสมา ระดับอินซูลิน น้ำหนักตัว และ HOMA-IR หลังการรักษาด้วยยาต้านไวรัสชนิดออกฤทธิ์โดยตรงทั้งสามช่วงเวลาของการติดตาม (ค่าพีเท่ากับ 0.47, 0.48, 0.15, 0.53) ตามลำดับ เมื่อสิ้นสุดการรักษาและ 6 เดือนหลังสิ้นสุดการรักษาพบว่าค่าเฉลี่ยของร้อยละ HOMA-IR ลดลงในกลุ่มที่มีภาวะดื้ออินซูลินเปรียบเทียบกับการเพิ่มค่าเฉลี่ยของร้อยละ HOMA-IR ในกลุ่มที่ไม่มีภาวะดื้ออินซูลินอย่างมีนัยสำคัญ (-25.4 เทียบกับ 356.4; ค่าพีเท่ากับ 0.003; -17.7 เทียบกับ 139.3; ค่าพีเท่ากับ 0.018) การอักเสบตับและค่าพังผืดเนื้อตับลดลงอย่างมีนัยสำคัญเมื่อสิ้นสุดการรักษา (ALT 113 เป็น 58 ยูนิต/ลิตร, ค่าพีน้อยกว่า 0.001; 21.3 เป็น 15.9 กิโลปาสคาล, ค่าพีน้อยกว่า 0.0001)

สรุป: การรักษาด้วยยาต้านไวรัสชนิดออกฤทธิ์โดยตรงในผู้ป่วยไวรัสตับอักเสบซีเรื้อรังที่ไม่เป็นเบาหวาน และมีภาวะดื้ออินซูลินจะช่วยให้ภาวะดื้ออินซูลินดีขึ้นโดยไม่สัมพันธ์กับการลดลงของน้ำหนัก