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Insulin Resistance in Patients with Chronic Hepatitis C Infection

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Abstract: Chronic HCV infection has emerged as a complex multifaceted disease with manifestations extending beyond the liver. Hepatic steatosis, insulin resistance (IR) and type II diabetes have been observed to occur more frequently in association with HCV infection than other chronic inflammatory liver disease. Insulin resistance is more often seen in hepatitis C than in other liver disease, including non-alcoholic steatohepatitis. Insulin resistance (IR) promotes liver fibrosis as hyperinsulinemia per se stimulates the proliferation of stellate cells enhancing the secretion of extracellular matrix. Moreover, hyperinsulinemia stimulate the expression of connective tissue growth factor. On the other hand, HCV is directly associated with IR in a dose-dependent manner as viral eradication after antiviral treatment may lead to an improvement of insulin resistance. The aim of this work is to study the relation between patients with CHC infection and insulin resistance. The study was conducted on 50 non diabetic patients with CHC and 10 age, sex, BMI matched group as a control. Complete history taking and clinical examination specially to examination of blood pressure, jaundice vascular spiders, liver flaps BMI, acanthosis nigricans, clinically detectable organomegaly or ascites, laboratory investigations including fasting serum glucose, fasting insulin, AST, AIT, Tbil and PT. *Results* showed that the means of fasting serum insulin, fasting serum glucose, serum AIT and AST were statistically higher in patients with HCV compared to the control. HOMA IR was found to be higher in patients with HCV than control with value of 4.9+1.6 and 0.99+0.28 respectively. HOMA is founded to be statistically related to BMI and serum. glucose and nearly significant to HCV (correlation coefficient 0.23 p-value 0.09). HCV was found to be significantly related to serum glucose, and HOMA. Linear regression analysis revealed that BMI and HCV infection were significant predictors for high HOMA level P 0.001, R seg : 0.617 which means that the regression model is significant and could explain 61.7% of change in HOMA level. In conclusion insulin resistance is common in patients with HCV. *Recommendation* monitoring and follow-up of serum glucose is important in euglycemic CHC patients. Study of vascular risk in CHC patients with metabolic IR is important and needed to be clarified.

Key words:

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, affecting 3% of the world's population, both HCV liver disease and type 2 diabetes are two already prevalent diseases that will probably continue to increase in the next decades (Lecube *et al*., 2006).

HCV mainly affects the liver, but also several tissues outside the liver have been reported to be involved, resulting in a wide spectrum of extrahepatic manifestations. During the last decade, it has been hypothesized that diabetes could be one more of these extrahepatic conditions attributable to HCV infection. This raises the intriguing question of whether the rise in HCV infection is contributing to the increasing prevalence of type 2 diabetes (Nocente *et al*., 2003).

Insulin sensitivity varies greatly within the general population. Factors contributing to this variability include genetic predisposition, obesity, unfavorable body fat distribution and lack of physical activity. Impaired insulin sensitivity may lead to impaired glucose tolerance and even in individuals with modest insulin deficiency to the development of type a diabetes mellitus of equal concern in patients with impaired insulin sensitivity is the development of the insulin resistance syndrome, in which hypertension, dyslipidemia, and impaired glucose tolerance form a cluster of risk factors for cardiovascular disease (Zachary, 1998).

Insulin resistance (IR) is known to be associated with the visceral adipose tissue area. Initially, in patients with insulin resistance, increased insulin secretion helps to maintain euglycemia as it compensates for the

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body's reduced biologic response to insulin. However, overtime, hepatic glucose output is increased in both the fasting and postprandial states. This, coupled with reduced glucose disposal from the circulation, contributes to elevated blood glucose (Reaven, 1995).

Elucidation of the relationship between hepatitis C virus (HCV) and IR is of great clinical relevance (Yoneda *et al*., 2007). The Homeostasis Model for Assessment HOMA = fasting insulin mul/mL x fasting glucose mmol/L 22.5 has proved useful in the measurement of insulin sensitivity in euglycemic patients. Cross-sectional and case-cohort studies support the role for hepatitis C as a factor implied in the development of type-2 diabetes in high risk patients (male patients, older than 40 years and overweight). Insulin resistance has been associated with steatosis development and fibrosis progression in a genotype-dependent manner. In genotype-1 patients, the mechanisms by which insulin resistance promotes fibrosis progression include: steatosis, hyperleptinemia, increased TNF production and impaired expression of PPAR, receptors (Romero, 2006).

Hui *et al*. (2003) reported that HCV subjects without a history of diabetes mellitus had significantly higher levels of all markers of IR, including fasting glucose, insulin, C peptide and HOMA-IR compared with healthy volunteers. On the other hand, several studies have reported that both insulin resistance and diabetes can adversely affect the course of chronic hepatitis C leading to enhanced steatosis and liver fibrosis and even increase the risk of hepatocellular carcinoma. Notably, it has recently shown that insulin resistance is an independent predictor of a poor response to antiviral therapy in chronic hepatitis C infection (Camma *et al*., 2006).

Chronic HCV infection have significantly increased prevalence of type a DM compared to controls or HBV-infected patients, independent of the presence of cirrhosis. Recently, the initial mechanisms involved in diabetes development in HCV infection have been evaluated, and we have provided evidence that non-diabetic HCV-infected patients have higher insulin resistance than patients with other chronic liver diseases and that this was associated with the activation of the TNF-a system and high IL-6 levels (Lecube *et al*., 2006).

It is postulated that an overabundance of circulating non esterefied fatty acid NEFA, mainly derived from adipose tissue, is a very early and major contributor to the development of insulin resistance. Recent studies have demonstrated that adipocytes synthesize and secrete biologically active molecules. These chemical messengers, collectively known as adipocytokines include tumor necrosis factor, adiponectin, resistin and Leptin (Yamauchi *et al*., 2001).

HCV infection is now recognized as a systemic disease involving lipid metabolism, oxidative stress and mitochondrial function. Risk factor for developing diabetes in HCV patients include positive family history of diabetes, advanced age high BMI, black ethnicity. Although 2 hours post-prandial insulin and 2 hours PP glucose are not considered markers of IR, yet in this study levels of 2 hrs pp insulin were higher than controls.

MATRIALS AND METHODS

The study included 50 non diabetic average weight patients with chronic hepatitis C and 10 age, sex and BMI normal matched control.

Exclusion Criteria:

All the studied subjects are not known to have diabetes mellitus or liver cirrhosis, must not have HBV infection determined by hepatitis B surface antigen and core antibody. Full medical history stressing on past history of blood transfusion, intravenous drug use, needle stick injury or sharing infected syringes. Thorough clinical examination stressing on blood pressure measurements, acanthosis nigricans and BMI (kg/m^2), jaundice, vascular spider, liver flaps, clinically detectable organomegaly or ascites.

Laboratory investigations including complete blood count fasting and post prandial blood sugar levels fasting and blood insulin level, alanine aminotransferase, serum bilirubin prothrombin time and concentration, blood urea, serum creatinine, lipid profile. Abdominal ultrasonography was done to all patients to document liver size and echo pattern. Diagnosis of chronic hepatitis C infection is based on persistent elevation of liver enzymes more than 6 months and liver biopsy for some of the patients and detection of HCV by PCR.

Calculation of IR using HOMA IR equation assessment of diabetic state according to the diabetes control and complications trial research group, 1993.

Calculation of Ir Using Homa-ir Equation:

HOMA-IR = F. insulin (uU/mL) x FBG (mmol/L)/22.5.

Principle of measurement of fasting blood insulin levels using ELISA. The DRG insulin ELISA Kit is a

solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle. The microtiter wells are coated with a monoclonal antibody directed towards a unique antigenic site on the insulin molecule. The standards are calibrated against international WHO approved reference material NIBSC 66/304, HCV by PCR quantitatively and liver biopsy for some patients.

Statistical Analysis:

Data were statistically described in terms of range, mean + standard deviation (+SD), frequencies (number of cases) and percentages when appropriate. Comparison between the study groups was done using Chi square (X^2) test. Exact test was used in stead when the expected frequency is less than 5. A probability value (P-value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2003 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results:

The mean serum blood glucose was 6.3 mmol/L +1.37 and 2.08+0.53mmol/lit in patients and control respectively. The mean fasting serum insulin in patients was 17.05 IU/L + 0.3 whereas in the control it was 10.69+1.3IUL/L.

HOMA IR was 4.9+1.69 and 0.99+0.28 in patients and control respectively. The mean BMI was 26.85+4.02 in the patients while it was 27.75+3.6 in the control group (Table 1). There was near statistically significant positive correlation between HCV and insulin resistance P-value 0.098 and near significant positive correlation between the mean serum glucose and HCV P-value 0.063 (Table 2-5).

Linear regression analysis revealed that BMI and HCV infection were significant predictors for high HOMA level P 0.001, R seg : 0.617 which means that the regression model is significant and could explain 61.7% of change in HOMA level (Table 6).

Table 1: Descriptive data of the patients and control

	HCV groupMean +SDn=50	ControlMean +SDn=10	P-value
Serum glucose mmol/l	6.3+1.3	2.08+0.53	0.000
Creatinine 0.6-1.3mg/dl	0.89 ±0.186	1.1 ± 0.25	0.273
Triglyceride 40-200 mg/dl	102.65 ±42.14	154.87 ± 60.08	0.048
Total cholesterol <200 mg/dl	116.25 ±27.28	156.47 ± 36.89	0.021
HDL-cholesterol >35 mg/dl	49.05 ±6.89	45.53 ± 6.36	0.326
Serum insulin IU/L	17.05+3.03	10.69+1.3	0.000
ALT mg %	34.45+11.63	23.9+10.65	0.000
AST mg %	50.5+13.23	44.8+9.1	0.000
HOMA IR	4.9+1.69	0.99+0.28	0.000
BMI	26.8+4.02	27.75+3.6	0.9

Table 2: Correlation between BMI to different variables

	Correlation coefficient	P-value
Serum glucose mmol/l	0.587	0.000
Serum insulin IU/L	0.33	0.018
HOMA IR	0.514	0.000
HCV	0.097	0.5
AST	-0.236	0.099

Table 3: Correlation between serum glucose to different variables

	Correlation coefficient	P-value
Serum insulin IU/L	0.6	0.000
HOMA IR	0.9	0.000
HCV	0.265	0.06

Table 5: Correlation between HCV to different variables

	Correlation coefficient	P-value
Glucose	0.26	0.06
Insulin	0.193	0.17
HOMA	0.237	0.098

Table 6: Regression analysis of HOMA

	Regression coefficient	P-value
BMI	0.20	0.000
HCV	3.9	0.000
ALT	0.017	0.29
AST	0.005	0.7

Discussion:

HCV infection is now recognized as a systemic disease involving lipid metabolism, oxidative stress, and mitochondrial function (Moucari *et al*., 2008). It was reported that the incidence of diabetes mellitus in adults with CHC and CHB (25% and 22.5%) respectively and is four times higher than that in the general population *(Custro et al., 2001)*. Patients with chronic hepatitis have impaired glucose metabolism with hyperinsulinemia and insulin resistance. This hyperinsulinemia has been shown to be due to decreased insulin catabolism rather than increased pancreatic insulin secretion. Up to 60% - 80% of patients with cirrhosis have glucose intolerance and about 20% eventually develop frank diabetes mellitus. A marked insulin resistance is common in patients with liver disease and represents a causative factor for the impaired glucose metabolism seen in these patients (Greco *et al*., 2002). In our results, the mean fasting serum insulin in patients was 17.05 IU/L + 0.3 whereas in the control it was 10.69+1.3.

Hui et al., (2003) reported that HCV patients without history of diabetes mellitus had significantly higher levels of all markers of IR including fasting glucose, fasting insulin and HOMA IR. In our results, the mean serum blood glucose was 6.3 mmol/L +1.37 and 2.08+0.53 in patients and control respectively. HOMA IR was 4.9+1.69 and 0.99+0.28 in patients and control respectively. Most of the studies indicate an independent higher prevalence of diabetes mellitus type II and/or insulin resistance in chronic HCV patients compared to control groups while in others this association was only confirmed in the presence of confounding factors. Antiviral treatment may lead to an improvement of insulin resistance is a strong argument in favor of a causal relationship between HCV infections and the presence of diabetes mellitus II (Imazcki *et al*., 2008). HOMA has been considered completely normal and higher than as pre-diabetic states (Romero, 2006).

Several mechanisms could explain the role of insulin resistance in the development of hepatic fibrosis. Hyperinsulinemia per se stimulates the proliferation of stellate cells, thus enhancing the secretion of extracellular matrix. Moreover, both insulin and hyperglycemia are able to stimulate the expression of connective tissue growth factor (Paradis *et al*., 2001).

On the other hand tumor necrosis factor TNF-a levels are elevated in the liver and serum of patients with chronic HCV infection specially genotypes 1 and 4. TNF-a plays an important role in the development of IR through interfering with insulin signaling in IR. In HCV core transgenic mice, treatment with anti TNF-a restored insulin sensitivity. Impairment of IRS-1 and IRS-2 expression HCV core protein inhibit insulin induced phosphorylation of P 85 subunit of phosphatidyl inositol 3 kinase HCV has been reported to mediate dysfunction of the insulin signaling pathways. Viral eradication after antiviral treatment may lead to an improvement of insulin resistance.

Recommendations:

Monitoring and follow-up of serum glucose level in the fasting and postprandial states is of important issue in euglycemic CHC patients. CHC infection should be evaluated as a systemic disease and not only as a liver disease. Study of cardiovascular risk in patients with CHC may be g value in insulin resistant patients..

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