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Frequency of Insulin Resistance Among Hepatitis C Virus Patients With or Without Oesophageal Varices

KEYWORDS: HCV, Insulin resistance, Oesophageal varices, HOMA

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ABSTRACT *Background: Insulin resistance (IR) is directly associated with the severity of fibrosis in chronic hepatitis C virus (HCV) patients. HCV associated with IR may cause enhanced hepatic steatosis, resistance to anti-viral treatment, faster progression of hepatic fibrosis and cirrhosis with development of portal hypertension and oesophageal varices (OV). Aim of the work: The aim of this study is to estimate the frequency of IR among patients with HCV related cirrhosis with or without OV in an attempt to clarify the role of IR as a risk factor for developing OV in cirrhotic patients.*

Patients and methods: This study was performed on 120 patients with HCV related cirrhosis; 60 of them had endoscopic evidence of OV and 60 without OV. All patients included in this study were subjected to full history taking, thorough physical examination, laboratory investigations (complete blood count, liver function tests, anti- HCV antibodies, PCR for HCV, lipid profile, fasting and post prandial blood glucose, fasting insulin level with calculation of Homeostasis Model Assessment (HOMA) test to assess insulin sensitivity of the patients), abdominal ultrasonography and Esophagogastroduodenoscopy (EGD).

Results: The frequency of IR was significantly higher among OV patients when compared to non-OV patients (61.7% vs 33.3% P<0.001). The mean HOMA test value was significantly higher in OV patients than non- OV patients (3.41±0.96 vs 2.49±0.88 P<0.001). Patients with IR had significantly higher frequency of large OV (grade 3 and 4) than patients with normal insulin sensitivity (35.1% and 27% vs 17.4% and 4.3% P=0.01).

Conclusion: Patients with OV secondary to HCV-related cirrhosis had higher frequency of IR when compared to those without OV. Patients with IR had larger OV than those with normal insulin response.

Introduction:
Oesophageal varices are serious consequence of portal hypertension, and variceal bleeding is a severe complication occurring in up to 50% of patients with cirrhosis. Despite improvement in diagnosis and therapy, mortality from acute variceal bleeding may reach up to 20%. Moreover, it is the second most common cause of death in cirrhotic patients [1]. Current guidelines recommend that all cirrhotic patients should be screened for varices at diagnosis, with follow up every 2-3 years for patients without varices and 1-2 years for patients with small varices to assess the enlargement of varices and the need for prophylactic treatment [2].

Insulin resistance is frequently seen in patients with HCV infection. Although in the general population, lack of exercise and overeating are major causes of IR, in patients with HCV infection, hepatic inflammation, activated inflammatory cytokines, and HCV-induced impairments of insulin and lipid signaling molecules are also important factors for the development of IR [3].

Aim of the work:
This study aimed at clarifying the relation between IR and development of OV in patients with chronic HCV related cirrhosis.

Patients and methods:
This study was done in Tropical medicine, Internal medicine and clinical pathology departments, Zagazig University Hospitals, in the period from April 2013 to July 2014it included 120 patients with chronic HCV infection who were classified into 2 groups:

- Group I: Child A or B patients with OV.
- Group II: Child A or B patients without OV.

Inclusion criteria:-
Patients with chronic HCV infection (child A or B).

Exclusion criteria:-
Patients with advanced cirrhosis (Child-Pugh class C), evidence of cholestasis, other causes of liver disease or mixed causes, diabetic patients or patients with peri-portal fibrosis by ultrasonography.

All cases were subjected to complete history taking Through clinical examination, laboratory investigations (CBC, Liver function tests, Serum uric acid, Lipid profile (TG and cholesterol), Fasting and postprandial blood glucose, Anti-HCV antibodies, HBsAg, Bilharzial Antibody titre and Autoimmune markers e.g. AMA, ANA, SMA, LKM).

N.B The severity of the liver dysfunction was graded according to Child-Pugh classification [4].

Child-Pugh classification.

Measure	1 point	2 points	3 points
Total Bilirubin	<2 mg/dl	2-3 mg/dl	>3 mg/dl
Serum albumin	>3.5 g/dl	2.8-3.5 g/dl	<2.8 g/dl

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INR	<1.7	1.71-2.20	> 2.2
Ascites	None	Suppressed with medication	Refractory
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

	Points	Class
	5-6	A
	7-9	B
	10-15	C

1- HOMA test to assess insulin sensitivity of the patients:

HOMA IR = Fasting insulin (μU/mL) x fasting glucose (mmol/L)/22.5. Mean HOMA IR score of 2.06 ± 0.14 in non-diabetic population and cut off value of HOMA-IR= 3 [5]

HOMA-IR has been validated in comparison with the euglycemic / hyperinsulinemic clamp technique in non-diabetic subjects [6], Abdominal ultrasound and EGD.

Classification of OV according to Paquet system [7] -:

- Grade 0: No Varices.
- Grade I: Varices disappearing with insufflations.
- Grade II: Varices is larger, clearly visible, usually straight, not disappearing with insufflations.
- Grade III: Varices is more prominent, locally coil-shaped, partly occupying the lumen.
- Grade IV: Varices is tortuous, sometimes grape-liked shape, occupying the lumen.

Statistical analysis:

Data were expressed as mean ± SD for quantitative data and number and percentage for qualititative data and comparison was done by paired t test (*) for the quantitative data and Chi-square teat X^2 (#) for categorial and qualitative data.Linear regression was used to evaluate correlation between variables.

Results:

Table (1): Demographic data.

Parameter		Group I N=60	Group II n=60	Test Value	P	Sig.
Age		53.11 ± 7.24	50.48 ± 8.61	1.81 *	0.07	NS:
Sex	Females	16 (26.7 %)	27 (45 %)	4.38 #	0.06	NS:
	Males	44(73.3 %)	33(55 %)			

Table (2): Comparison between studied groups as regards all clinical, laboratory and endoscopic data

HB (g/dl)		11.65 ± 1.41	13.65 ± 1.43	7.67*	0.001	HS
PLT count (cell/uL)		66.86 ± 13.28	152.15 ± 26.81	22.07*	0.001	HS
Albumin (g/dl)		3.11 ± 0.46	3.63 ± 0.32	6.99 *	0.001	HS
Bilirubin (mg/dl)		1.54 ± 0.77	1.18 ± 0.63	2.82 *	0.06	NS
ALT (IU/L)		92.83 ± 41.99	55.33 ± 39.13	5.06 *	0.001	HS
AST(IU/L)		74.26 ± 35.32	42.48 ± 31.44	5.20 *	0.001	HS
PT (sec.)		13.01 ± 1.14	12.29 ± 1.32	3.17*	0.02	S
INR		1.29 ± 0.11	1.20 ± 0.14	3.85*	0.001	HS
Spleen size (cm)		15.75 ± 2.38	14.3 ± 1.96	3.45 *	0.001	HS
Portal vein diameter (mm)		12.32 ± 1.03	11.95 ± 0.94	2.06 *	0.04	S
Ascites	No	50 (83.3 %)	54 (90 %)	1.15 #	0.28	NS
	Mild	10 (16.7 %)	6 (10 %)			
Child grade	A	40 (66.7 %)	52 (86.7 %)	6.7#	0.001	HS
	B	20 (33.3 %)	8 (13.3 %)			
Triglycerides (mg/dl)		137.01 ± 27.81	99.06 ± 32.68	6.84*	0.001	HS
Cholesterol (mg/dl)		141.35 ± 29.07	143.08 ± 21.72	0.37*	0.71	NS
Serum uric Acid (mg/dl)		6.83 ± 1.66	6.59 ± 1.68	0.79*	0.43	NS
Fasting blood sugar		95.85 ± 14.96	95.80 ± 15.69	0.01*	0.98	NS
Post prandial blood sugar		159.51 ± 19.92	162.31 ± 19.15	0.78*	0.43	NS
Portal hypertensive gastropathy	0	32 (53.3 %)	55 (91.7 %)	23.84#	0.001	HS
	1	16 (26.7 %)	5 (8.3 %)			
	2	9 (15 %)	0(0%)			
	3	3 (5 %)	0(0%)			
Gastric varices	No	56 (93.3 %)	60 (100 %)	2.66#	0.11	NS
	Yes	4 (6.7 %)	0(0%)			
IR	Yes	37 (61.7 %)	20 (33.3 %)	9.65*	0.001	HS
	No	23 (38.3 %)	40 (66.7 %)			
HOMA		3.41 ± 0.96	2.49 ± 0.88	5.7 #	0.001	HS

Table (3): comparison between the studied groups as regards level of viremia

Viremia	Group I N=60		Group II N=60		X^2	P	Sign.
	No	%	No	%			
Low	28	46.66%	35	58.33			
Moderate	22	36.66%	17	28.33	1.2	0.21	NS
High	10	16.68%	8	13.34			

Table (4): correlation between HOMA-IR and OV grades, gastric varices and portal hypertensive gastropathy in group I:

Parameter IR		HOMA IR No IR		X^2	P	Sig.
OV Grades	1	8 (21.6 %)	11 (47.8.7 %)	9.95	0.01	S:
	2	6 (16.2 %)	7 (30.4 %)			
	3	13 (35.1 %)	4 (17.4 %)			
	4	10 (27 %)	1 (4.3 %)			
Gastric varices	No	33 (89.2 %)	23 (47.8.7 %)	2.66	0.1	NS
	Yes	4 (10.8 %)	0			

Table (5): Correlation between HOMA with other parameters in group I:

	R	P	Sig.

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Age	0.10	0.42	NS
WBCs	0.08	0.53	NS
HB	0.00	0.95	NS
PLT	0.21	0.10	NS
PT	0.09	0.47	NS
INR	0.08	0.53	NS
Albumin	0.22	0.08	NS
Bilirubin	0.18	0.15	NS
ALT	0.04	0.73	NS
AST	0.05	0.66	NS
Level of viremia	0.03	0.41	NS
Triglycerides	0.10	0.42	NS
Cholesterol	0.09	0.47	NS
Uric Acid	0.06	0.64	NS
Portal vein diameter	0.06	0.64	NS
Spleen size	0.11	0.40	NS
Child score	1	0.16	NS
Portal hypertensive gastropathy	0.36	<.001	HS:

Table (6): Correlation between HOMA with other parameters in group II.

	R	P	Sig.
Age	0.05	0.69	NS
WBCs	0.15	0.23	NS
HB	0.02	0.83	NS
PLT	0.09	0.47	NS
PT	0.16	0.19	NS
INR	0.14	0.26	NS
Albumin	0.19	0.12	NS
Bilirubin	0.24	0.06	NS
ALT	0.10	0.42	NS
AST	0.11	0.40	NS
Level of viremia	0.04	0.81	NS
Triglycerides	0.02	0.85	NS
Cholesterol	0.03	0.77	NS
Uric Acid	0.10	0.44	NS
Portal vein diameter.	0.001	0.94	NS
Spleen size	0.15	0.24	NS
Child score	1	0.16	NS
Portal hypertensive gastropathy	0.15	0.23	NS

Discussion:

Insulin resistance enhances fat deposition inside the hepatocytes which related to defect of the mitochondrial pathway of fatty acids metabolism. This will eventually leads to steatosis, non-alcoholic fatty liver disease, and non-alcoholic steatohepatitis [8,9]. HCV is incriminated in causing IR in patients with chronic hepatitis C. Moreover, IR enhanced fat deposition in the liver can hasten the progression of HCV associated liver injury and enhances the development of cirrhosis. It became well known now that IR and the resultant hepatic steatosis even have a bad impact on HCV response to interferon therapy [10,11]. Several studies in chronic liver diseases have shown a strong and independent pathogenic link between IR and HCV infection [12,13] and between IR and the severity of hepatic fibrosis[14,15].

This study aimed at clarifying the relation between IR and development of OV in patients with chronic HCV related cirrhosis. The relation can be rationalized by the fact that insulin resistance with HCV can lead to faster progression to fibrosis and cirrhosis and hence early appearance of complications.

Comparing the patients with OV with the control group, we found that there was no significant difference between the two groups as regards age and gender distribution. This was in agreement with most of the related literature that stated that age and gender have no effect on the development of OV [16,17,18].

In our study, we found that the OV group of patients had also significantly lower blood parameters i.e. Hemoglobin concentration, WBCS counts, platelet count. This can be easily explained by the fact that many of them had previous bleeding episodes; also OV group of patients had significantly larger spleen size than the control group so these decreased blood parameters can also be the result of hypersplenism. This was in agreement with Sarangapani et al, 2010) who found that patients with thrombocytopenia are more likely to have OV than patients with normal platelet count [17].

In our study, patients with OV had significantly lower serum albumin level, higher PT and INR, higher liver enzymes and hence higher child's grade and score than the control group and this agrees with most of the related literature. Albumin level is considered by Bressler et al, 2005 to be a non-invasive predictor of OV [19].

The study by Schepis et al, 2001 agreed with ours that high PT level is a good predictor of OV[20]. However, the study by Giannini et al, 2006 found that there was no relation between PT and OV [21]. Moreover, high Child's grade and score were considered by Zaman et al, 2001 to be also a risk factor for developing OV [22].

However, patients with OV in our study had no significant difference in their bilirubin level when compared to the control group. This disagrees with Bressler et al, 2005 who considers higher bilirubin to be a predictive factor for OV [19], this disagreement may be because patients with evidence of cholestasis were excluded from our study. This finding as regards bilirubin agreed with Giannini et al, 2006 who found no relation between bilirubin and the presence of OV [21].

There was no significant difference as regards ascites between the test and the control groups. This finding disagrees with the study Ng et al, 1999 which claims that presence of ascites and presence of OV are strongly related. [23], this disagreement as regards ascites may be because most of the patients in our study had no or just minimal ascites.

In this study we found that patients with OV had spleenomegaly and significantly wider portal vein diameter than the control group. This agreed with Madhotra et al, 2002 who considerd spleenomegaly a strong sign of portal hypertension and predictor for the presence of OV [24]. Our study agreed with the study of Schepis et al, 2001 who reported that the wider the portal vein the higher the incidence of OV[20]. Patients with OV had also higher incidence of portal hypertensive gastropathy than the control group. This is easily justified by the fact that all the evidence show that OV group of patients had significantly higher portal pressure and worse liver functions than the control group.

As regards IR, patients with OV in our study had significantly higher HOMA-IR mean value. They also had significantly higher frequency of IR than the control group. Patients who were diagnosed with IR by HOMA-IR in our

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study in both groups had significantly higher grade of OV than those without IR. This means that the insulin resistance is not only associated with the development of OV but also linked to its severity.

Proving the relation of IR to OV among all these differences and variables between test and control groups was difficult. Most of these parameters are considered non-invasive predictors of OV and matching patients according to all these variables was nearly impossible. It became a must that we prove that IR and HOMA-IR level is totally independent from any other parameter that could be related to the presence of OV. In our study, there wasn't any significant correlation between HOMA-IR level and any of the hematological parameters. HOMA-IR had no significant correlation to albumin level, bilirubin level, liver enzymes levels, PT, INR, ascites degree, or child's grade or score in both studied groups. HOMA-IR had no significant correlation to spleen size or portal vein diameter. However, it had a significant correlation to the presence of portal hypertensive gastropathy in the test group. This proves that HOMA-IR is totally independent from the other factors that affects and predicts the development of OV and hence insulin resistance alone is considered a risk factor for developing OV. This is agreed with by Camma et al, 2009 who studied HOMA-IR as another non-invasive predictor for the presence of OV [25].

Conclusion:

From all the previous results it was concluded that the frequency of IR and the HOMA value are significantly higher in patients with OV and patients with IR have higher frequency of higher grades of OV than patients with normal insulin sensitivity.

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