Serum Resistin and Insulin Resistance as Risk Factors for Hepatocellular Carcinoma in Cirrhotic Patients with Type 2 Diabetes Mellitus

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Abstract: Background: Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer related death. At least 25% of HCC cases do not have any known etiology. Approximately 2-fold higher risk of HCC in diabetic patients. The causal nature of this positive association involves complex mechanisms that have not yet been conclusively described. Previous studies have suggested that elevated levels of insulin and insulin growth factor (IGF) may play important roles in HCC. Resistin is a polypeptide hormone belonging to adipokines and could contribute to tumorigenesis and angiogenesis. Aim: to study serum resistin and insulin resistance as risk factors for HCC in hepatitis C virus (HCV) cirrhotic patients with type 2 diabetes mellitus.

Subjects and Methods: 50 adult patients with HCV infection were selected for this study. They were categorized into: (Group I) which included 25 type 2 diabetes mellitus (DM) patients with cirrhosis and HCC and (Group II) which included 25 type 2 DM patients with cirrhosis only. 25 healthy subjects, age and sex-matched, were enrolled as controls (Group III). Routine tests for DM, HCV, liver cirrhosis & HCC were done. HOMA-IR and serum resistin were assessed in all groups. Results: HCC diabetic patients (Group I) showed significantly higher mean values of HOMA-IR and resistin than cirrhotic diabetic patients (Group II) and the control subjects (Group III). Frequency of low value for HOMA-IR index (>2.5) was not significantly different between HCC (Group I) and cirrhotic (Group II) patients but Frequency of high value for HOMA-IR index (>4) was significantly different between HCC and cirrhotic patients with higher frequency in HCC patients (Group I) (76%) when compared with cirrhotic patients (Group II) (4%). In HCC patients (Group I), significant positive correlations were found between HOMA-IR and both fasting insulin and α - Fetoprotein (AFP). Significant positive correlations were found between resistin, and both fasting insulin and AFP. Positive correlation was found between HOMA-IR & resistin in (Group I) & (Group II). Conclusions: HOMA-IR and serum resistin measurement could represent novel markers to identify the HCV cirrhotic patients with type 2 DM at greater risk for the development of HCC. These findings may have important prognostic and therapeutic implications as insulin resistance (IR) is a potentially modifiable factor.

Key words: Hepatocellular Carcinoma, Hepatitis C virus, Insulin resistance, Resistin, Type 2 Diabetes Mellitus

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Globally, it is the sixth most common cancer and the third leading cause of cancer related death. Recognized risk factors for HCC are hepatitis C virus (HCV) and hepatitis B virus (HBV) infections, and alcohol consumption; however, at least 25% of HCC cases do not have any known etiology. The burden of HCC has been increasing in Egypt with a doubling in its incidence rate in the past 10 years. It is the second most frequent cancer type in Egyptian males after bladder cancer. The high incidence of HCC in Egypt is attributed to the high prevalence of HCV. Type 2 Diabetes is also a prevalent disease with an increasing incidence globally. It is widely recognized that there is a positive association between HCC and diabetes mellitus, with an approximately 2-fold higher risk of liver cancer in diabetic patients. The causal nature of this positive association involves complex systematic mechanisms that have not yet been conclusively described.

Insulin is produced exclusively by pancreatic β cells and transported to the liver via the portal vein, resulting in a high concentration of endogenously produced insulin in the liver. Previous studies have suggested that elevated levels of insulin and insulin growth factor (IGF) may play important roles in hepatic fibrosis and fibrosis progression and HCC. In addition, diabetes plays a role in the development of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis, which are believed to induce HCC via progression of cirrhosis.
Resistin is a polypeptide hormone belonging to adipokines \(^{14}\). It was called resistin because of the observed insulin resistance in mice injected with resistin \(^{14}\). Resistin acts as intrahepatic cytokine exerting pro-inflammatory actions \(^{12}\). Several recent studies have indicated that resistin may significantly influence the growth and proliferation of malignant cells \(^{13}\). Although only a few studies have analyzed resistin in patients with malignancies, the general properties of resistin could contribute to tumorigenesis and angiogenesis \(^{14}\).

Our aim was to study serum resistin and insulin resistance as risk factors for HCC in HCV cirrhotic patients with type 2 diabetes mellitus.

2. Subjects and Methods

Study Population

This prospective study was conducted with 75 participants divided into three groups. The first group (Group I) comprised 25 type 2 diabetic patients with HCV liver cirrhosis and hepatocellular carcinoma (HCC). The second group (Group II) comprised 25 type 2 diabetic patients with HCV liver cirrhosis. A third group (Group III) included 25 apparently healthy participants (non diabetic with normal liver) as control group. This study was conducted at Tanta University Hospital, Internal Medicine department, between June 2013 and June 2014. This study was conducted in accordance with the guidelines of the Declaration of Helsinki and its subsequent amendments. Written consent was obtained from all participants prior to enrollment in the study and all were mentally and physically capable of answering a questionnaire.

Exclusion criteria included, Obesity (BMI ≥30), concurrent human immunodeficiency virus infection, HBV, active alcohol consumption, Previous history of treatment with interferon therapy for HCV, any treatment for HCC, current treatment with any dosage of insulin therapy, treatment with corticosteroids or any medications known to affect glucose tolerance or insulin secretion.

Study design, biochemical assays and radiological investigations:

All subjects were submitted to detailed history taking including age, sex, occupation, special habits, risk factors for liver diseases such as previous HCV and history of diabetes mellitus including the duration and type of antidiabetic therapy and clinical assessment with particular focus upon the manifestations of stigmata of chronic liver disease, organomegaly and ascites. BMI was calculated as body weight in kilograms divided by the square of height in meters (kg/m\(^2\)). Liver cirrhosis was diagnosed on the basis of history, clinical examination, laboratory findings, and abdominal ultrasonography (US). HCC was diagnosed by abdominal (US), abdominal triphasic CT and serum AFB \(^{15}\). Diabetes mellitus was diagnosed using the American Diabetes Association criteria \(^{16}\).

Morning 12-hours overnight fasting and 2 hours postprandial venous blood samples (5 ml) were collected by trained laboratory technicians. Fasting and 2 hours postprandial blood glucose level and HbA1c were measured by using Synchron CX4 clinical system. Alanine Transaminase (ALT) and Aspartate Transaminase (AST) were measured by colorimetric method using kits provided by Biomerieux laboratory reagents and instrument, France. Serum bilirubin was measured by colorimetric method using kits provided by Boehringer Mannheim Gmbh Diagnostica. Serum albumin was measured by using kits provided by AMES division, MILES laboratories limited, England. Sera of all patients and controls were tested for hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (anti-HBc) and anti-HCV antibodies by ELISA, using third generation kits (DiaSorin, Italy). α– Fetoprotein (AFP) was estimated by serological techniques (Axyam System, Abbott Laboratories). Fasting plasma insulin was measured by the electrochemiluminescence immunoassay "ECLIA" on an analyser (Roche Diagnostic Gmbh, USA). Serum level of Resistin was measured using the Quantikine Human Resistin Immunoassay ELISA kit (Cat. No: DRSN00, Europe, United Kingdom). Insulin resistance was assessed by the Homeostasis Model Assessment method (HOMA). The HOMA index of insulin resistance (HOMA-IR) was calculated on the basis of fasting values of plasma glucose (FPG) and fasting insulin (FI), as follows: [FPG (mg/dl) x FI (μU/mL)] /405. Patients were called HOMA-IR (+) if their HOMA scores were higher than 2.5, denote low insulin sensitivity (insulin resistance) \(^{17}\). The HOMA-IR index has seen widespread use, with various cut-off values for insulin resistance. In many studies of Caucasian populations a cut-off value of 2.5 has been applied; other studies have used higher cut-off values \(^{18}\). Genetic variation with respect to different ethnic groups will influence choice of cut-off value \(^{19}\); for this study we also used a cut-off value of 4.0 (high value for HOMA-IR) \(^{20}\).

Radiological investigations including abdominal ultrason and triphasic contrast enhanced computed tomography scan of the abdomen to confirm HCC.

Statistical analysis

The collected data were tabulated and analyzed using SPSS version 17 software (SPSS Inc, Chicago, ILL Company). Categorical data were presented as number and percentages while quantitative data were expressed as mean and standard deviation. Comparison of continuous data between two groups was made by using unpaired t-test for parametric data.
and Mann-Whitney test for nonparametric data. Comparison of continuous data between more than two groups was made by using one way ANOVA for parametric data and Kruskal-Wallis test for nonparametric data. Fisher’s exact and Chi-square tests were used for comparison between Categorical data. Spearman & Pearson tests for correlations between different parameter (nonparametric & parametric respectively) were used. The accepted level of significance in this work was stated at 0.05 (P <0.05 was considered significant).

3. Results

Baseline characteristics

(Table 1): Ages of HCC diabetic patients (Group I) (mean 53.92 years; range 43-65 years), cirrhotic diabetic patients (Group II) (mean 52.92 years; range 40-66 years) and control group (Group III) (mean 51.4 years; range 38-63 years) were closely comparable, while Preponderance of males was observed with both HCC (Group I) and cirrhotic groups (Group II); 1: 3.17 and 1: 2.13 female: male ratio respectively. There was no significant difference between all groups regarding age or sex (p = 0.3902 and 0.9868, respectively). No significant difference was observed in BMI between the studied groups (p = 0.0806).

Biochemical characteristics

(Table 2) HCC diabetic patients (Group I) showed significantly higher mean values of ALT, total bilirubin, direct bilirubin, and AFP than cirrhotic patients (Group II) (p = 0.0160, 0.0053, 0.0177, <0.0001 respectively). Other parameters showed insignificantly difference between (Groups I & Group II).

(Table 3) HCC diabetic patients (Group I) showed significantly higher mean values of FPG, fasting insulin, HOMA-IR and resistin than cirrhotic patients (Group II) and the control subjects (Group III) (p <0.0001 for all).

(Table 4) Frequency of low value for HOMA-IR index (>2.5) was not significantly different between diabetic HCC (Group I) and cirrhotic (Group II) patients but Frequency of high value for HOMA-IR index (>4) was significantly different between HCC and cirrhotic patients with higher frequency in HCC patients (Group I) (76%) when compared with cirrhotic patients (Group II) (4%).

(Table 5) In HCC diabetic patients (Group I), significant positive correlations were found between HOMA-IR and both fasting insulin and AFP. Also, significant positive correlations were found between serum resistin and both fasting insulin and AFP. In cirrhotic diabetic patients (Group II), significant positive correlations were found between HOMA-IR and age, fasting insulin and FPG. Also, significant positive correlations were found between serum resistin and both fasting insulin and FPG. In HCC diabetic patients (Group I) and cirrhotic diabetic patients (Group II), significant positive correlations were found between HOMA-IR & resistin.

Table (1): Demographic data of the studied groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I HCC diabetic group (N=25)</th>
<th>Group II Cirrhotic diabetic group (N=25)</th>
<th>Group III Control group (N=25)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male (number) (%)</td>
<td>19 (76%)</td>
<td>17 (68%)</td>
<td>20 (80%)</td>
</tr>
<tr>
<td></td>
<td>Female (number) (%)</td>
<td>6 (24%)</td>
<td>8 (32%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean±SD</td>
<td>53.92±5.999</td>
<td>52.92±7.371</td>
<td>51.4±6.028</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>Mean±SD</td>
<td>21.99±0.926</td>
<td>22.42±0.8944</td>
<td>22.41±0.8846</td>
</tr>
</tbody>
</table>

Table (2): Laboratory characteristics among the patients groups (I & II).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I HCC diabetic group (N=25)</th>
<th>Group II cirrhotic diabetic group (N=25)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (U/L)</td>
<td>Mean±SD</td>
<td>86.76±23.854</td>
<td>71.76±18.102</td>
</tr>
<tr>
<td>AST(U/L)</td>
<td>Mean±SD</td>
<td>79.52±18.583</td>
<td>74.6±18.283</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>Mean±SD</td>
<td>3.49±1.58</td>
<td>2.39±0.9878</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>Mean±SD</td>
<td>2.1±1.28</td>
<td>1.38±0.6768</td>
</tr>
<tr>
<td>Serum Albumin (g/dl)</td>
<td>Mean±SD</td>
<td>2.86±0.3736</td>
<td>3.07±0.5697</td>
</tr>
<tr>
<td>Serum AFP (ng/ml)</td>
<td>Mean±SD</td>
<td>539.84±260.58</td>
<td>44.08±36.501</td>
</tr>
<tr>
<td>PPG (mg/dl)</td>
<td>Mean±SD</td>
<td>259.24±57.346</td>
<td>255.08±36.492</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>Mean±SD</td>
<td>8.96±1.215</td>
<td>8.42±1.338</td>
</tr>
</tbody>
</table>
Table (3): Fasting plasma glucose, fasting insulin HOMA-IR and serum resistin among the studied groups.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>157.76 ± 46.64</td>
<td>150.56 ± 44.618</td>
<td>91.28 ± 6.093</td>
<td>&lt;0.0001*</td>
<td>0.5578</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>21.96 ± 19.336</td>
<td>7.14 ± 2.558</td>
<td>3.26 ± 0.9082</td>
<td>&lt;0.0001*</td>
<td>0.0001*</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>HOMA-IR (U/L)</td>
<td>8.02 ± 6.669</td>
<td>2.61 ± 1.081</td>
<td>0.74 ± 0.225</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Resistin (ng/ml)</td>
<td>6.11 ± 1.654</td>
<td>3.11 ± 1.533</td>
<td>1.31 ± 0.3198</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
<td>0.0001*</td>
</tr>
</tbody>
</table>

P1 group I vs. II  P2 group I vs. III  P3 group II vs. III

Table (4): Frequency of low and high value for HOMA-IR index (>2.5) and (>4) respectively in patients groups (group I & II).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I HCC diabetic group (N=25)</th>
<th>Group II Cirrhotic diabetic group (N=25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA-IR index (&gt;2.5)</td>
<td>+ve 20 (80%)</td>
<td>14 (56%)</td>
<td>0.1284</td>
</tr>
<tr>
<td></td>
<td>-ve 5 (20%)</td>
<td>11 (44%)</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR index (&gt;4)</td>
<td>+ve 19 (76%)</td>
<td>1 (4%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td></td>
<td>-ve 6 (24%)</td>
<td>24 (96%)</td>
<td></td>
</tr>
</tbody>
</table>

Table (5): Correlation between (HOMA-IR) & resistin and different variables of the patients groups (group I & II).

<table>
<thead>
<tr>
<th>Variables</th>
<th>HOMA-IR</th>
<th>Resistin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
<td>Group II</td>
</tr>
<tr>
<td></td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.1897</td>
<td>0.3638</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>0.9138</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>0.009696</td>
<td>0.6447</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>-0.2143</td>
<td>0.3036</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>-0.1487</td>
<td>0.4780</td>
</tr>
<tr>
<td>Serum Albumin (g/dl)</td>
<td>-0.06794</td>
<td>0.7469</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.07857</td>
<td>0.7089</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dl)</td>
<td>0.1353</td>
<td>0.3191</td>
</tr>
<tr>
<td>Serum AFP (ng/ml)</td>
<td>0.5885</td>
<td>&lt;0.002*</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.3814</td>
<td>0.8564</td>
</tr>
<tr>
<td>PPG (mg/dl)</td>
<td>0.06006</td>
<td>0.7755</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>0.2076</td>
<td>0.3194</td>
</tr>
<tr>
<td>HOMA-IR (U/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistin (ng/ml)</td>
<td>0.5146</td>
<td>0.0008*</td>
</tr>
</tbody>
</table>
4. Discussion

Insulin resistance is a pathological condition in which insulin action is impaired in peripheral target tissues including skeletal muscle, liver, and adipose tissue (21). Patients with insulin resistance show an increased morbidity and mortality, largely attributable to cardiovascular disease and Type 2 DM (22,23). Moreover, a number of epidemiological studies have consistently demonstrated that the risk for several types of cancer is higher in insulin-resistant patients (24).

Our aim was to study serum resistin and insulin resistance as risk factors for HCC in HCV cirrhotic patients with type 2 diabetes mellitus.

In our study, ages of HCC patients (Group I) (mean 53.92±5.999 years; range 43-65 years), These results were in concordance with that of El-Zayadi AR et al., 2005 (25) who studied 1328 patients with HCC in the period between the years 1993 to 2002 and found that the age of those patients ranged from 40 to 59 years. Our finding is close to Abdel-Wahab M et al., 2007 (26) who reported a male to female ratio 2.8:1 in a study performed on 403 HCC cases at NCI, Egypt. Also El-Zayadi AR et al., 2005 (25) who documented that male to female ratio was 5:1. Abdel-Wahab M et al., 2007 (26) as well reported that male to female ratio was 5:1 in their study which was performed in Lower Egypt. This male predominance was also observed by Lehman EM et al., 2008 (29) who stated that male to female ratio was 4:1 in their study which was carried out in Gharbiah Population-Based Cancer Registry, Egypt, on 1186 patients with HCC. The difference in age & male: female ratio was due to different sample sizes.

In our study, HCC patients (Group I) showed insignificantly higher mean values of AST and PPG than cirrhotic patients (Group II), and insignificantly lower mean value for albumin. HCC patients (Group I) also showed significantly higher mean values of ALT, total bilirubin and direct bilirubin when compared to cirrhotic patients (Group II). Mohamed AA et al., 2011 (30) showed that HCC patients had significantly lower median value for albumin, significantly higher median value of bilirubin and Insignificant differences were found between HCC and cirrhotic patients regarding median values of ALT, glucose. On the other hand, HCC patients showed significantly higher
median value of AST when compared to cirrhotic patients.

In the present study, HCC patients (Group I) showed significantly higher mean value of AFP when compared to cirrhotic patients (Group II). Also, Arrieta O et al., 2007 (51) and Mohamed AA et al., 2011 (30), stated that AFP level was significantly higher in patients with HCC compared to patients with liver cirrhosis.

In our study, HCC patients (Group I) showed insignificantly higher mean value of HbA1c, than cirrhotic patients (Group II). Donadon et al., 2010 (32) reported that HbA1c level in patients with HCC is higher than in patients with liver cirrhosis. Also Mohamed AA et al., 2011 (30), stated that HCC patients had significantly higher median value HbA1c, than cirrhotic patients. In patients with liver cirrhosis HbA1c does not properly represent glycemic control status because of the short lifespan of erythrocytes caused by hypersplenism (33,34). These data indicate that assessment and management of diabetes mellitus in cirrhotic patients using HbA1c is inaccurate.

Our results showed that, HCC patients (Group I) showed significantly higher mean values of fasting insulin and HOMA-IR, than cirrhotic patients (Group I) and the control subjects (Group III). Frequency of low value for HOMA-IR index (  2.5) was not significantly different between HCC (Group I) and cirrhotic (Group II) patients but Frequency of high value for HOMA-IR index ( 4) was significantly different between HCC and cirrhotic patients with higher frequency in HCC patients (Group I) (76%) when compared with cirrhotic patients (Group II) (4%). In HCC diabetic patients (Group I), significant positive correlations were found between HOMA-IR and both fasting insulin and AFP. In cirrhotic diabetic patients (Group II), significant positive correlations were found between HOMA-IR and age, fasting insulin and FPG.

In consistent with that results, Donadon V et al., 2009 (35), found that the mean levels of HOMA-IR increase progressively among chronic hepatitis C (CHC), liver cirrhosis and HCC patients. Gomaa AA et al., 2010 (36), also found that Insulin and HOMA-IR were higher among HCC group than those with CHC alone matched for age, sex and BMI. Serum insulin and HOMA-IR were in both groups were higher than healthy volunteers. Elevated levels of IR occur regardless the presence of DM. Similarly Hung CH et al., 2010 (8), had demonstrated that IR is associated with high risk of HCC development in patients with chronic HCV. Patients with HCC had higher blood sugar, insulin level and HOMA-IR than those with chronic hepatitis and advanced fibrosis. Patients with HCC had a higher ratio of HOMA-IR  4 (61.8%) than those with chronic hepatitis (39.5%) and advanced fibrosis (48.8%). Similar results were proved by Nkontchouemail G et al., 2010 (37), who reported that in patients with compensated HCV cirrhosis, high HOMA-IR index was associated with HCC occurrence, and it was a strong predictor of liver related death or transplantation. Mohamed FS et al., 2014 (38), showed that HOMA-IR was significantly higher in intermediate/advanced stage HCC patients, compared to early stage HCC and HCV-positive cirrhotic patients respectively.

On the other hand, Mohamed AA et al., 2011 (39), who investigated the effects of HCV genotype-4 on the prevalence of IR in CHC and HCC Egyptian patients. HCC patients showed no significant differences were found between HCC and CHC patients regarding median values of glucose, fasting insulin, and HOMA-IR index values. Frequency of high value for HOMA-IR index ( 4) was not significantly different between CHC and HCC patients (52% vs. 40%). Irshad M et al., 2013 (39), also found that IR is significantly raised in all disease groups as compared to control group. However they could not find a significant difference in IR level on mutual comparison of any two disease groups. This implies that difference in IR values obtained for chronic viral hepatitis (CVH) vs. Cirrhosis, CVH vs. HCC and Cirrhosis vs. HCC was non-significant. The value of IR was also analyzed in different disease groups comparing simultaneously in relation to HBV and HCV infection. They observed that as such, there was not a definite trend of IR level obtained in relation to disease or causative virus and majority of HCC patients (72.7%) had IR level of more than 3, though it was not significantly different in HBV and HCV induced HCC.

Several hypothesis which could explain this relationship, Alexia C et al., 2004 (40), suggested that hyperinsulinemia which occur in IR can promote the synthesis and biological activity of insulin-like growth factor 1 (IGF-1), which is a peptide hormone that regulates energy-dependent growth processes. IGF-1 stimulates cell proliferation and inhibits apoptosis and has been shown to have strong mitogenic effects on a wide variety of cancer cell lines. Changes in the expression pattern of IGF-system components have been observed in patients with HCC, in human HCC cell lines and in their conditioned culture medium, as well as in rodent models of hepatocarcinogenesis.

Serum resistin is proportionally related to cancer development, including: breast and colorectal cancers. It has also been suggested that the expression of resistin in cancer cells is associated with more malignant clinicopathological processes (41,42). However, there is still a lack of information about the precise mechanisms of resistin on HCC development.
Our results showed that, HCC patients (Group I) showed significantly higher mean value of serum resistin than cirrhotic patients (Group I) and the control subjects (Group III). In HCC patients (Group I), significant positive correlations were found between resistin, and both fasting insulin and AFP. 

Yagmur E et al., 2006 (43) and Kakizaki S et al., 2008 (44) demonstrated that, resistin serum levels were significantly elevated in patients with liver cirrhosis compared with healthy controls. Yagmur E et al., 2006 (43) showed that resistin increased with stage of liver cirrhosis as defined by Child-Pugh or model for end-stage liver disease (MELD) score. Serum resistin correlated with insulin secretion (C-peptide) and inversely with insulin sensitivity (HOMA-index) in chronic liver disease patients. Kakizaki S et al., 2008 (44) showed that resistin showed significantly positive correlation with fasting plasma insulin, HOMA-IR index. The plasma resistin levels did not correlate with sex, body mass index and fasting plasma glucose levels. Yang CC et al., 2014 (45) clarify the role of resistin in inducing HCC cells adhesion to the endothelium and demonstrate the inhibitory effect of adenosine monophosphate (AMP-activated protein kinase activation under the resistin stimulation, so resistin may play an important role to promote HCC metastasis.

Conclusions

HOMA-IR and serum resistin measurement could represent novel markers to identify the HCV cirrhotic patients with type 2 DM at greater risk for the development of HCC. These findings may have important prognostic and therapeutic implications as IR is a potentially modifiable factor.

We recommend large scale multicenter studies covering the different Egyptian population to better clarify the diagnostic performance of HOMA-IR and serum resistin.

There are some limitations to our study. First, the analysis was carried out in a cross-sectional setting with a relatively small number of HCC patients, and it would be interesting to determine whether this association holds true in longitudinal follow-up studies of larger groups of patients. Another limitation lies in the fact that there is some concern on the use of HOMA-IR in the presence of long-standing DM. However, a diagnosis of DM is per se expression of IR, and HOMA-IR is a less invasive, inexpensive, and less labor-intensive method to measure IR.

Competing interests:
All The authors declare that they have no competing interests.

Author contributions:
All authors contributed equally to this work.

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