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The Role of Insulin Resistance in the Prediction of Esophageal Varices in Cirrhotic Nondiabetic Patients

Abdelhaleim Abdelghany Hasabo, Mahmoud Osama Ahmed Abd El Fatah, Mohamed Basiouny Yahia, Gamal Zakaria Ali Morsy

Abstract

Background: Esophageal Varices (EV) caused by liver cirrhosis is a very common complication where endoscopy is the best screening procedure. Insulin resistance (IR) is a reliable predictor of portal hypertension.

Aim of the work: This study aims to compare and evaluate the role of markers of IR and other non-invasive markers in the detection of EVs in patients with liver cirrhosis.

Patients and methods: Fifty patients were screened in this cross-sectional study in the gastroenterology unit of the internal medicine department by abdominal ultrasound. ELISA technique was used to estimate fasting serum insulin levels. Furthermore, (HOMA-IR) referring to the Homeostasis model assessment of IR was carried out.

Results: Cirrhotic patients whether they possessed any grade of EV or not correlated with higher IR with their platelet count/spleen diameter ratio (PC/SD) and spleen diameter showing a statistically significant difference among the groups.

Conclusion: Elevations in IR (as they were assessed by HOMA-IR) were found to be good predictors of the development of EVs noninvasively. The diameter of the Portal vein (PV), the diameter of the spleen, and PC/SD were also found to be good predictors of EVs.

Keywords: Diabetes mellitus, Esophageal varices, Insulin resistance

1. Introduction

During the course of Type 2 Diabetes Mellitus, which accounts for about 90 percent of all cases of diabetes, the body’s response to insulin is not adequate, as such this condition is known as Insulin Resistance (IR). The sequelae include hyperglycemia, cardiovascular system impairment, chronic inflammation, misbalance in oxidative stress status, and occurrence of metabolic syndrome. Despite the advanced progress in understanding molecular and metabolic pathways accounting for the harmful effects of IR towards multiple organs, IR is still recognized as a doubtful problem. The number of many available therapeutic approaches is growing, however, the need for perfect, safe, and effective therapy is also in need. IR, or decreases in cellular response succeeding insulin stimulation, happens due to complex genetic and environmental factors that play a significant role in the pathogenesis of type 2 diabetes. IR was linked with obesity, as adipose tissue produces mediators which were linked to insulin sensitivity decrease, as an example, elevated levels of free fatty-acid within circulation are usually seen associated with obesity, reducing insulin sensitivity through acting at a number of levels in the signaling cascade. Chronic, low-grade inflammatory processes are characterized by increases in inflammatory signaling and the production of cytokines in association with IR and abnormalities in metabolic processes. As these metabolic abnormalities persist, obesity and over nutrition being examples, they contribute to states of chronic, low-grade inflammation and lead to an overexpression of a number of inflammatory mediators in obesity. Endoscopic sclerotherapy is not the first choice because of its association with an increased risk for complications; as a result, its use should be limited only to situations where venous ligation therapy is not available or is technically impossible. Other endoscopic modalities,
such as endoscopic clipping, argon plasma coagulation, and microwave ablation, have no established role for esophageal varices (EV) management because the evidence is not clear and lacks validation by prospective study. The use of TC-325 haemostatic powder for variceal hemorrhage carries a risk for gas embolization, and its use is currently off-label. However, it can be considered as a bridge therapy with developed protocols. Insulin regulates the synthesis of endothelin and nitric oxide in the endothelium, which are important regulators of blood flow in the sinusoids. Consequently, IR leading to hepatic vasoconstriction and fibrosis can be considered as possible mechanisms for the development of EVs. The homeostasis model assessment (HOMA model) was initially developed in 1985 by Matthews et al. and It was used as a tool to measure insulin and beta-cell function tolerance using the concentrations of fasting levels of both insulin (or C-peptide) and glucose. Since then, the HOMA model has been deemed a highly successful clinical and epidemiological method for the assessment of IR. The study was aimed to assess the impact of IR on the development of EV in HCV-related liver disease.

2. Patients and methods

Fifty patients were selected from inpatients admitted to the Sayed Galal university hospital from April 2022 to October 2022 and diagnosed as chronic hepatitis C patients with associated diabetes mellitus type II and hematemesis. Patients known to have DM and obese ones were not included in the study. Patients of etiologies of liver disease or with a mixed etiology, portal vein thrombosis patients, Malignancy patients or those with any endocrinal disorders, in addition to those with a body mass index exceeding or equal to 30 kg/m² were no included in the study.

All patients went through full history taking, full clinical examinations and abdominal ultrasound with TOSHPA machine. All patients fasted for at least 8–12 h before examination. The examination was conducted with the use of 3.5 or 5 MHZ transducers; occasionally a 5 or 7.5 MHZ transducer was used to evaluate the surface of the liver.

Laboratory investigations were done including liver function tests, CBC, serum albumin, insulin level using electrochemiluminescence immunoassay method using Hitachi cobase-411, fasting plasma glucose and IR by the Homeostatic Model Assessment (HOMA-IR), which was calculated as:

\[
\text{Fasting insulin (uIU/ml) \times Fasting plasma glucose (mg/dl)}
\]

With a Reference range: up to 3.4.

All patients study underwent upper endoscopy: The procedure was performed at Bab Elsharia Hospital endoscopic unit using Olympus GIF type 2 T 200 videoscope, flexible endoscope.

The patients were categorized to patients with and without EV and the EV patients were classified according to the degree of varices. EV were classified into 4 grades regarding their size at the gastro esophageal junction in accordance with Westbay et al. in 1993 into Grade 1 as Varices were flush with the surface of the oesophagus, Grade 2 as Protrusion of the varices but foe less than half way to the center of the lumen, Grade 3 as Protruding varices exceeding half way to the lumen and Grade 4 as the varices were large enough to meet at the midline.

2.1. Statistical analysis of data

The data were analyzed with the use of the software: SPSS Statistics Desktop, V21.0.0; which is a word processing, database and statistics program. Ethical considerations: The nature of the study was explained to all patients and a verbal consent was obtained.

3. Results

Table 1.
Most of the study patients are grade I EV (80%) and only 20% grade II EV Table 2.

There was significant difference between patients with EV grade 1 and grade 2 regarding to HOMA-IR Tables 3 and 4.

There was a correlation between laboratory parameters as platelet count, serum albumin, fasting blood sugar, fasting insulin, portal vein diameters and HOMA-IR.

There was high significant difference between study groups regarding to fasting blood sugar, fasting insulin and HOMA Table 5.

There was significant difference between study groups regarding to MBSD, PVD and platelet/splenic diameters.

4. Discussion

Portal hypertension is seen as one of the most common and important complications of liver cirrhosis. The formation and progression of EV is considered a clinical presentation of portal
hypertension with a prevalence ranging up to 80% in cirrhotic patients. The clinical presentations of EV are linked to the bleeding risk with mortality rates more than 20% within 6 weeks from the bleeding attacks despite the standard treatment. Screening for esophageal and gastric varices using endoscopy must always be done when a diagnosis of cirrhosis is sure by sonar and pathology. Upper GIT endoscopy should be repeated every 2-year interval in patients who don't have varices and on an annual basis in patients who have small varices to evaluate their development or progression. IR is often seen in patients infected with the hepatitis C virus and the incidence rate of IR is higher in patients with hepatitis C infection in comparison with the general population and patients with other hepatic diseases. An association has been made with IR, advanced fibrosis and its development in several studies. In our study Fifty (50) patients with liver cirrhosis were included and divided into two groups according to the presence or absence of EV on upper GIT endoscopy. It was discovered that parameters with a link to portal hypertension (platelet count, MSBD, PVD and platelet/splenic diameter ratio) in addition to those parameters related to liver dysfunction (serum albumin and prothrombin time) were associated with the presence of any EV.

Table 1. Frequency of grade I and II among the positive endoscopic patients regarding to esophageal varices grades.

<table>
<thead>
<tr>
<th>Endoscopy</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>40 (80%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>10 (20%)</td>
</tr>
</tbody>
</table>

Table 2. Correlations between grade I and grade II varices regarding to HOMA –IR (Homeostatic Model Assessment of Insulin Resistance).

<table>
<thead>
<tr>
<th>Esophageal grade</th>
<th>N</th>
<th>HOMA</th>
<th>Independent t-test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>40</td>
<td>3.19</td>
<td>0.55</td>
<td>2.277</td>
</tr>
<tr>
<td>Grade II</td>
<td>10</td>
<td>3.80</td>
<td>0.59</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Correlations between (HOMA-IR) and the studied and recorded parameters in patients groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HOMA-IR</th>
<th>r</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yrs)</td>
<td>0.226</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Platelets $10^9$/mm$^3$</td>
<td>$-0.244$</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>Serum Albumin (gm/dl)</td>
<td>$-0.246$</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dl)</td>
<td>0.774</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Fasting Insulin (ulu/ml)</td>
<td>0.597</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Portal vein diameter (cm)</td>
<td>0.565</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Comparative study between patients with and without esophageal varices regarding FBS, F. insulin and (HOMA-IR).

<table>
<thead>
<tr>
<th></th>
<th>With EV group</th>
<th>Without EV group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. = 40</td>
<td></td>
<td>No. = 40</td>
<td>80</td>
</tr>
<tr>
<td>Fasting blood suger (mg/dl)</td>
<td>95.30 ± 19.11</td>
<td>90.55 ± 11.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting Insulin (ulu/ml)</td>
<td>16.56 ± 2.39</td>
<td>15.39 ± 2.29</td>
<td>0.030</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.88 ± 0.66</td>
<td>3.15 ± 0.53</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Our study was in agreement with other studies which document that there is high significant suffERENCE and correlations between the EV and IR and all the manifestations of portal hypertension. From our study, we find also the following: HOMA-IR ratio showed very good results in discriminating between patients with no EV and those with EV particularly in non-obese and non-diabetics.

HOMA-IR ratio was found in significant correlations with a number of noninvasive parameters proven to predict EV’s presence. As hepatitis C is a common disease in Egypt and the high incidence of type II diabetes mellitus in Egyptian populations, IR in hepatitis c virus patients with cirrhosis measured by the HOMA-IR formula has a significant role in predicting the presence of EVs in these patients and can be utilized as non-invasive parameter to predict EVs.

The previous study was in agreement with our study as we work on the same patients groups. It was found that the presence of EVs has an independent association with decreased platelet counts and a raised HOMA index. The previous statements were in agreements with our results finding.

Wasfy et al. reached a conclusion that measuring IR by HOMA-IR disregarding the existence of diabetes is a significant predictor of the presence of EVs which agrees with our study.

Table 5. Comparative study between study groups regarding to MSBD, Portal vein diameter and platelet/splenic diabetes.

<table>
<thead>
<tr>
<th></th>
<th>With EV group</th>
<th>Without EV group</th>
<th>Independent t-test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. = 40</td>
<td></td>
<td>No. = 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSBD (cm) Maximal splenic bipolar diameter</td>
<td>Mean ± SD</td>
<td></td>
<td>3.059</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>140 ± 21</td>
<td>150.76 ± 16.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVD (cm)</td>
<td>Mean ± SD</td>
<td></td>
<td>3.287</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>14.9 ± 1.8</td>
<td>14.1 ± 2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets/splenic diameter</td>
<td>Mean ± SD</td>
<td></td>
<td>3.399</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>1035 ± 400</td>
<td>760 ± 314.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A value of HOMA-IR exceeding 3.5, independent of the presence of diabetes, is a significant predictor of the occurrence of EVs in cirrhotic patients. 27

4.1. Conclusion

Higher IR and lower insulin sensitivity assessed by (HOMA-IR) and (QUIKI) respectively are good noninvasive predictors of EVs. Additionally, PC/SD, PV diameter and the diameter of the spleen are found to be predictors of EV.

Disclosure

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Authorship

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Conflicts of interest

The authors declared that there were no conflicts of Interest.

References