Insulin resistance in patients with cirrhosis and portal hypertension

Eva Erice,1,2 Elba Llop,1,3 Annalisa Berzigotti,1,2 Juan G. Abraldes,1,2 Ignacio Conget,4 Susana Seijo,1 Enric Reveret,1 Agustín Albillos,2,5 Jaume Bosch,1,2 and Juan Carlos García-Pagán1,2

1Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clinic, Institut d’Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain; 2Centro de Investigación Biomèdica en red de Enfermedades Hepáticas y Digestivas, Barcelona, Spain; 3Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain; 4Endocrinology and Diabetes Unit, Hospital Clinic, Institut d’Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; and 5Gastroenterology Unit, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria, University of Alcalá, Madrid, Spain

Submitted 22 September 2011; accepted in final form 3 April 2012

Insulin resistance in patients with cirrhosis and portal hypertension. Am J Physiol Gastrointest Liver Physiol 302: G1458–G1465, 2012. First published April 5, 2012; doi:10.1152/ajpgi.00389.2011.—Insulin resistance (IR) is involved in the pathogenesis of endothelial dysfunction and is also present in patients with cirrhosis. Intrahepatic endothelial dysfunction plays a major role, increasing hepatic vascular resistance and promoting portal hypertension (PH). In addition, β-adrenergic agonists and insulin share several intracellular signaling pathways. Thus IR may influence the response to β-blockers. This study aimed at evaluating the relationship between IR and hepatic hemodynamics in patients with cirrhosis and with the portal pressure response to acute β-blockade. Forty-nine patients with cirrhosis and PH were included. Hepatic and systemic hemodynamics were measured, and IR was estimated by using the updated homeostasis model assessment (HOMA)-2 index. Patients with HOMA-2 > 2.4 were considered IR. In patients with hepatic venous pressure gradient (HVPG) ≥ 10 mmHg [clinically significant PH (CSPH)], hemodynamic measurements were performed again 20 min after intravenous propranolol. Mean HOMA-2 index was 3 ± 1.4. Fifty-seven percent of patients had IR. A weak correlation between HOMA-2 index and HVPG was observed. Eighty-six percent of patients had CSPH. HOMA-2 index was an independent predictor of CSPH. However, in patients with CSPH, the correlation between HOMA-2 index and HVPG was lost. HVPG, but not IR, predicted the presence of esophageal varices. Response to propranolol was not different between patients with or without IR. In nondiabetic patients with cirrhosis, HOMA-2 index is directly associated with the presence of CSPH and indirectly with varices, but does not allow either grading HVPG or predicting its response to propranolol.

endothelial dysfunction; insulin signaling; portal pressure; β-blockade; homeostasis model assessment index

PORTAL HYPERTENSION (PH) is a serious consequence of cirrhosis that results in life-threatening complications with increased morbidity and mortality (3, 4, 22). In cirrhosis, enhanced hepatic resistance to portal blood inflow is the primary factor in the pathophysiology of PH. Second, an increased portal blood inflow contributes to the maintenance and worsening of PH, despite the development of portosystemic collaterals. Insufficient nitric oxide (NO) bioavailability in sinusoidal endothelial cells, a condition known as endothelial dysfunction, is considered a major pathogenic factor to increase hepatic vascular tone (27) and has shown to be secondary to several different posttranslational alterations in the regulation of hepatic endothelial NO synthase.

In addition to its metabolic action on glucose uptake, insulin also stimulates endothelial NO production, by activating the phosphatidylinositol 3-kinase and serine-threonine kinase (PI3K/Akt) signaling pathway (50). As a consequence, insulin resistance (IR) has been shown to result in impaired PI3K/Akt signaling pathway, causing a decrease in NO production, with the ensuing development of endothelial dysfunction (41) in several cardiovascular disorders, such as arterial hypertension, diabetes, and atherosclerosis (12, 36, 44).

IR has been described in several liver disorders (9, 14, 32, 39), where it may have important clinical consequences. Thus it has been suggested that IR has a negative impact on the response rates to interferon-based therapy in chronic hepatitis C virus infection (19) and that IR could be a predictor of the presence of PH in patients with nonalcoholic fatty liver disease (16). Furthermore, a recent published clinical study has suggested that IR is able to independently predict the presence of gastroesophageal varices in cirrhosis (11). The authors attributed this effect to a possible pathophysiological link between IR and PH. IR could contribute to either impairment of the sinusoidal endothelial dysfunction, or increment of peripheral vascular resistance in liver cirrhosis. Therefore, a possible effect of IR on the hepatic vasculature promoting an increase in intrahepatic resistance may be counteracted by a potential effect of IR increasing splanchnic resistance and reducing portal blood flow, with a resulting unpredicted effect on portal pressure. Unfortunately, up to now, there is no study evaluating the relationship between IR and hepatic and systemic hemodynamics in liver cirrhosis.

The current pharmacological therapy for PH is nonselective β-adrenergic blockers (5). Several factors influence the hepatic venous pressure gradient (HVPG) response to β-blockers, such as the degree of liver failure, dose of β-blockers, extent of portal-systemic collaterals, and varices or β2-adrenoceptor gene polymorphisms (1, 2, 8, 15, 17, 47). IR could represent another component in this multifactorial phenomenon. Vascular relaxation in response to β2-adrenoceptor agonists involves two components (24, 49): one endothelium independent, mediated by the activation of the cyclic AMP dependent-protein kinase A pathway in vascular smooth muscle cells; and another endothelium dependent, mediated by the activation of the PI3K/Akt signaling pathway that leads to NO release. As mentioned, this pathway is shared with insulin signaling (13, 34). A possible downregulation of this pathway by IR could interfere with the β-adrenergic signaling. Hence, it is plausible
that IR may represent an additional factor influencing the hemodynamic response to propranolol in patients with cirrhosis.

The main aim of this study was to investigate the potential relationship between IR and hepatic and systemic hemodynamics in patients with cirrhosis. As secondary endpoints, the value of IR predicting the presence of clinically significant PH (CSPH; defined as an HVPG ≥ 10 mmHg) and gastroesophageal varices, as well as the influence of IR on the hemodynamic response to acute β-adrenergic blockade, will be assessed.

PATIENTS AND METHODS

Patients
The study was performed in 49 out of 267 patients with cirrhosis, referred from May 2008 to February 2010 to the Hepatic Hemodynamic Laboratory for the evaluation of PH (Fig. 1). All patients were diagnosed with cirrhosis at the clinic, based on biological, ultrasonographic, or histological criteria. The extensive exclusion criteria were as follows: absence of PH (HVPG < 6 mmHg); pregnancy or lactation; cardiac, renal, or respiratory failure; hepatocellular carcinoma; portal vein thrombosis; previous surgical or transjugular portosystemic shunt; presence of infection or acute decompensation in the prior 2 wk; prescription of hypolipemiant, antihypertensive, corticosteroid, bronchodilator, vasoactive, or hypoglycemic agents within 1 mo. Patients with established diabetes or metabolic syndrome (defined by the International Diabetes Federation) were excluded to discard their probable direct effect on the IR component derived from liver cirrhosis.

The study was performed according to the principles of the Declaration of Helsinki. The Ethics Research Committee of the Hospital Clinic of Barcelona approved the protocol in May 2008. Informed, written consent to participate in the study was obtained for every patient.

Methods

Hemodynamic studies. After fasting overnight, patients were transferred to the Hepatic Hemodynamic Laboratory. In brief, a venous introducer was placed in the internal jugular vein by the Seldinger technique under local anesthesia. Under fluoroscopy, a Swan-Ganz catheter (Edwards Laboratory, Los Angeles, CA) was advanced into the pulmonary artery for measurement of cardiopulmonary pressures and cardiac output (CO) by thermal dilution. Subsequently, a 7F balloon-tipped catheter (Edwards Lifesciences Fogarty 7F, Los Angeles, CA) was guided into the main right hepatic vein to measure wedged and free hepatic venous pressure, as described by previous authors to obtain hepatic pressures (6, 21). Mean arterial pressure (MAP, mmHg) was measured every 5 min by a noninvasive automatic sphygmomanometer and the heart rate was derived from continuous electrocardiogram monitoring.

In the subgroup of patients with CSPH, a solution of indocyanine green (Pulsion Medical Systems, Munich, Germany) was infused intravenously at a constant rate of 0.2 mg/min, preceded by a priming dose of 5 mg. After an equilibration period of at least 40 min, four separates sets of simultaneous samples of peripheral and hepatic venous blood were obtained for the measurement of hepatic blood flow (ml/min) by the Fick principle, as previously described (26, 16a). In these patients, after baseline measurements, intravenous propranolol (0.15 mg/kg) was administered over 10 min, and hepatic and cardiopulmonary pressures, CO, and hepatic blood flow were assessed again after 20 min.

All measurements were taken by triplicatem and permanent tracings were obtained in a multichannel recorder (Mac-Lab/Specials Laboratory, General Electric Medical System). Portal pressure was estimated from HVPG (mmHg) as the difference between wedged and free hepatic venous pressure. Cardiac index (CI; l·min⁻¹·m⁻²) was calculated as CO/body surface area and systemic vascular resistance.
### Table 1. Baseline clinical and hemodynamic characteristics of the 49 patients included

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Non-IR Group</th>
<th>IR Group</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>49</td>
<td>19</td>
<td>30</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>27/22</td>
<td>11/8</td>
<td>16/14</td>
</tr>
<tr>
<td>Age, yr</td>
<td>57 ± 10</td>
<td>56 ± 9</td>
<td>58 ± 10.6</td>
</tr>
<tr>
<td>Active alcoholism, %</td>
<td>16</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.6 ± 5.7</td>
<td>24 ± 2</td>
<td>27 ± 4.6</td>
</tr>
<tr>
<td>Etiology, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>15</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>HCV</td>
<td>25</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>HBV</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Ascites, n</td>
<td>16</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Varices, n</td>
<td>28</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>Bilirubin, mg/dl</td>
<td>2.1 ± 2.1</td>
<td>1.3 ± 1.1</td>
<td>2.5 ± 2.4</td>
</tr>
<tr>
<td>Albumin, g/l</td>
<td>32 ± 6</td>
<td>33 ± 6.5</td>
<td>32 ± 5.5</td>
</tr>
<tr>
<td>Platelets, ×10⁹/l</td>
<td>103 ± 46</td>
<td>117 ± 49</td>
<td>94 ± 43</td>
</tr>
<tr>
<td>Prothrombin time, %</td>
<td>67</td>
<td>77 ± 15</td>
<td>60 ± 19</td>
</tr>
<tr>
<td>Child-Pugh class (A/B/C)</td>
<td>28/12/9</td>
<td>14/5/2</td>
<td>14/9/7</td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td>7 ± 2.1</td>
<td>6 ± 1.6</td>
<td>7.5 ± 2.3</td>
</tr>
<tr>
<td>MELD score</td>
<td>12.5 ± 5.2</td>
<td>10 ± 3</td>
<td>14 ± 5.6</td>
</tr>
<tr>
<td>HOMA-2 index</td>
<td>3 ± 1.4</td>
<td>1.6 ± 0.6</td>
<td>3.9 ± 1</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>5.6 ± 1</td>
<td>5.3 ± 1</td>
<td>5.8 ± 1</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td>144.5 ± 68.8</td>
<td>81.8 ± 27.5</td>
<td>191.5 ± 55</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>92 ± 14</td>
<td>94 ± 13.2</td>
<td>90 ± 14.7</td>
</tr>
<tr>
<td>CI, l·min⁻¹·m⁻²</td>
<td>3.7 ± 1.3</td>
<td>3.1 ± 0.6</td>
<td>4.02 ± 1.3</td>
</tr>
<tr>
<td>SVRI, dyn·s·m⁻²·cm⁻³</td>
<td>3,091</td>
<td>2,376 ± 553</td>
<td>1,881.6 ± 885</td>
</tr>
<tr>
<td>HVPG, mmHg</td>
<td>15.5 ± 6</td>
<td>13 ± 5</td>
<td>17 ± 5.5</td>
</tr>
<tr>
<td>CSPH, %</td>
<td>77.6</td>
<td>58</td>
<td>90</td>
</tr>
</tbody>
</table>

Continuous variables are means ± SD; n, no. of subjects. P values are non-insulin resistance (IR) vs. IR group. BMI, body mass index; HCV, hepatitis C virus; HBV, hepatitis B virus; MELD, model for end-stage liver disease; HOMA-2 index, homeostasis model assessment-2 index; MAP, mean arterial pressure; CI, cardiac index; SVRI, systemic vascular resistance index; HVPG, hepatic venous pressure gradient; CSPH, clinically significant portal hypertension.

Fig. 2. Relation between HOMA-2 index and HVPG in the 49 patients (A) and in the subgroup of 38 patients with clinically significant portal hypertension (B).
ascites, the body mass index (BMI) (kg/m²), was calculated using a

10% from baseline after intravenous propranolol administration were

is right atrial pressure). Patients exhibiting a decrease in HVPG

patients with and without CSPH

Active alcoholism, % 0 21 0.17

Age, yr 56 ± 12.4 58 ± 9.5 0.5

Active alcoholism, % 0 21 0.17

Etiology, n

Alcohol 0 15

HCV 8 17

HBV 3 3

Other 3 3

Ascites, n 0 16 0.009

Varices, n 0 28 0.00

Bilirubin, mg/dl 0.8 ± 0.2 2.5 ± 2.2 0.00

Albumin, g/l 36 ± 3.7 31 ± 5.4 0.017

Platelets, ×10⁹ 108 ± 46 102 ± 51 0.2

Esplenomegaly, % 55 79 0.2

Prothrombin time, % 85 ± 9.5 62 ± 18.2 0.00

Child-Pugh class (A/B/C) 11/0/0 17/12/0 0.04

Child-Pugh score 5 ± 1 7 ± 2 0.004

MELD score 7.6 ± 1.1 13 ± 5.1 0.00

HOMA-2 index 1.85 ± 1.2 3.4 ± 1.3 0.001

Glucose, mmol/l 5.2 ± 0.7 5.7 ± 1.1 0.15

Insulin, pmol/l 91.5 ± 58.2 160 ± 64.4 0.003

MAP, mmHg 97 ± 16.3 90 ± 13.7 0.038

CI, 1·min⁻¹·m⁻² 2.4 ± 1.5 4 ± 1.2 0.00

SVRI, dyn·s·m⁻²·cm⁻⁵ 2,800 ± 750 1,892.6 ± 651 0.00

HVPG, mmHg 8 ± 1 17.5 ± 5 0.00

Continuous variables are means ± SD; n, no. of subjects. P values are

HVPG <10 vs. HVPG ≥10 group.

index (SVRI, dyn·s·m⁻²·cm⁻⁵) as (MAP – RAP) × 80/CI (where RAP is

right atrial pressure). Patients exhibiting a decrease in HVPG ≥10%

from baseline after intravenous propranolol administration were

defined as “hemodynamic responders” (31, 48). In patients with

ascites, the body mass index (BMI) (kg/m²), was calculated using a

correction factor of 4 kg to estimate the real weight. It represents the

mean of evacuated liters in large-volume paracentesis (18, 40).

Evaluation of IR. IR was estimated from fasting plasma glucose

and insulin levels by using the updated homeostasis model assessment

(HOMA-2) index (35), and it was calculated using the HOMA-2

calculator, which is downloadable from The Oxford Centre for Dia-

betes, Endocrinology and Metabolism web site (www.dtu.ox.ac.uk).

HOMA is an index that estimates steady state β-cell function (%B)

and insulin sensitivity (%S). It has been previously validated in

healthy populations, noninsulin-treated type 2 patients, and people

with metabolic syndrome. Several studies suggest that HOMA index

could be an useful tool to identify subjects with IR at risk of

developing cardiovascular diseases (10, 29).

Eighty-two healthy normal-weight subjects (50 men and 32

women, age ranging between 28 and 48 yr) without family history of
diabetes mellitus were chosen to define the normal value of the

HOMA-2 index in our area. The upper 75% value of the HOMA-2

index was 2.4. Patients with HOMA-2 index above this value were

considered to have IR.

In the subgroup of patients with CSPH, the C-peptide-to-insulin

molar ratio in peripheral venous blood was used to estimate indirectly

insulin metabolism, as assessed previously (30, 35). In normal con-

ditions, insulin and C-peptide are secreted into the portal vein in a 1:1

molar ratio. The liver mainly clears endogenous insulin, whereas

C-peptide is cleared by the kidney in a lower metabolic clearance rate

than insulin. As a consequence, the C-peptide-to-insulin molar ratio

in peripheral venous blood is higher than 1.0 (7). Plasma free insulin

and C-peptide were measured by radioimmunassay.

In addition, blood samples from peripheral and hepatic veins were

obtained to measure NO products (NOx, NO₂⁻, NO₃⁻) by chemilumi-
ekence (Nitric Oxide Analyzer, NOA 280; Sievers Instruments, Boul-
der, CO) and von Willebrand factor (antigen vWF (Ag vWF)) by

europe linked immunosorbent assay system as a marker of endothe-

dial dysfunction.

Statistics

Statistics analyses were performed using SPSS 16.0 statistical package

(SPSS, Chicago, IL). All results are expressed as mean ± SD for

continuous variables and frequencies and percentages for categorical

variables. U Mann-Whitney was used to perform comparisons between

groups for continuous variables and Fisher test, test, and linear-by-linear

test for categorical variables. Correlation was performed by Rho’s Spear-

man coefficient. Statistical significance was established as P < 0.05.

Multivariable logistic regression models were constructed to look for

independent predictors of varices, CSPH and IR.

RESULTS

Clinical and Hemodynamic Characteristics of Patients With

Cirrhosis, With and Without IR

The baseline clinical and laboratory characteristics of the 49

patients included are shown in Table 1. Mean age was 57 yr,

and 55% were men. The most frequent etiology of cirrhosis

was hepatitis C virus infection (51%) and active alcoholism

...
was present in eight patients. Mean Child-Pugh score was 7 ± 2.1. The mean HOMA-2 index was 3 ± 1.4. Thirty of the 49 patients (61%) had a HOMA-2 index above the cutoff value defining IR (≥2.4) with a mean value of 4 (ranging from 2.5 to 6). As shown in Table 1, patients with IR had higher BMI, bilirubin, Child-Pugh, and model for end-stage liver disease (MELD) scores, CI, HVPG, and significantly lower systemic vascular resistance, platelets count, and prothrombin time than those without. Multivariate logistic regression analysis disclosed prothrombin time as the only independent predictor for the presence of IR.

**IR, HVPG, and CSPH**

A weak but significant correlation between HOMA-2 index and HVPG was observed (Fig. 2A; \( r^2 = 0.19, P = 0.02 \)). Thirty-eight of the 49 patients included (86%) had CSPH (Table 2). Correlation between HOMA-2 index and HVPG was lost when only patients with CSPH were considered (\( r^2 = 0.02, P = 0.29 \); Fig. 2B).

As shown in Table 2, patients with CSPH had significantly higher HOMA-2 index, more ascites, presence of esophageal varices (EV), and worse hepatocellular function than patients without CSPH. Multivariate analysis disclosed high HOMA-2 index and low prothrombin time as the only independent predictors for the presence of CSPH.

In the subgroup of 38 patients with CSPH (mean HVPG: 17.5 ± 5 mmHg; range: 10–31.5 mmHg), 27 patients were IR (71%) and 11 patients were not (29%). As shown in Table 3, prothrombin time, insulin, C-peptide, and SVRI were significantly different in patients with IR, without significant differences in hepatic or peripheral NOx or Ag vWF levels. However, no significant differences in HVPG were observed (HVPG: 18 ± 5 vs. 16 ± 4.5 mmHg, \( P = 0.39 \)). Multivariate analysis also disclosed prothrombin time in addition to BMI as independent predictors for the presence of IR in the subgroup of patients with CSPH. Interestingly, a significant inverse association between HOMA-2 and the C-peptide-to-insulin molar ratio (a surrogate of portal systemic shunting) was observed (\( r = -0.35, P = 0.04 \) (Fig. 3).

**IR and EV**

As shown in Table 4, patients with EV had a significantly higher MELD score, HOMA-2 index, CI, HVPG, and presence of CSPH and a significantly lower prothrombin time and SVRI than patients without EV. However, multivariate analysis disclosed that only HVPG independently predict the presence of EV, either evaluated as continuous variable or categorized in CSPH vs. non-CSPH.

| Table 4. Clinical and hemodynamic characteristics of the patients with or without gastroesophageal varices |
|-------------------------------------------------|-------------------------------------------------|-----------------|
| n                                               | Yes EV  | No EV  | \( P \) Values |
| Age, yr                                         | 58 ± 9.3  | 56 ± 10.8  | 0.28       |
| Active alcoholism, %                            | 18.5  | 13.6  | 0.71       |
| Bilirubin, mg/dl                                | 2.4 ± 2.2  | 1.8 ± 2  | 0.06       |
| Albumin, g/l                                    | 32 ± 6.4  | 34 ± 5.4  | 0.07       |
| Prothrombin time, %                             | 62 ± 18.2  | 73 ± 19  | 0.04       |
| Platelets, \( \times 10^9 \)                    | 105 ± 55  | 101 ± 33  | 0.2        |
| Child-Pugh class (A/B/C)                        | 12/9/6  | 16/3/3  | 0.1        |
| Child-Pugh score                                | 7 ± 2.1  | 6.5 ± 2  | 0.09       |
| MELD score                                      | 13.4 ± 4.7  | 11.2 ± 5.6  | 0.04       |
| HOMA-2 index                                    | 3.4 ± 1.3  | 2.5 ± 1.4  | 0.02       |
| Glucose, mmol/l                                 | 5.6 ± 1  | 5.6 ± 1.2  | 0.75       |
| Insulin, pmol/l                                 | 163.4 ± 62  | 121.3 ± 71  | 0.016      |
| MAP, mmHg                                       | 89 ± 11  | 97 ± 17  | 0.12       |
| CI, \( \text{min}^{-1} \cdot \text{m}^{-2} \)   | 4 ± 1.2  | 3.3 ± 1.4  | 0.016      |
| SVRI, \( \text{dyn} \cdot \text{s} \cdot \text{cm}^{-5} \) | 1,778 ± 547  | 2,469 ± 961  | 0.005      |
| HVPG (mmHg)                                     | 17.5 ± 5  | 13 ± 6  | 0.005      |
| CSPH (>10 mmHg), %                              | 96.3  | 54.5  | 0.001      |

Continuous variables are means ± SD; \( n \), no. of subjects. \( P \) values are yes esophageal varices (EV) vs. no EV group.
Acute HVPG Response to Propranolol

In the CSPH group (n = 38), acute propranolol administration produced a significant reduction in HVPG (−15%, P = 0.00) (Table 5). No significant correlation was found between HOMA-2 index and reduction in HVPG (r = −0.054, P = 0.6). There were no statistically significant differences in the hemodynamic response to acute intravenous propranolol in patients with or without IR (−15 ± 10.5 vs. −15 ± 11.5%, P = 0.39) (Table 5). The percentage of “hemodynamic responders” was similar in both groups (IR group 65% vs. without-IR: 64% P = nonsignificant).

DISCUSSION

Insulin is known to regulate glucose metabolism and NO production by activating endothelial NO synthase (50). Reduced secretion of NO, as a consequence of IR, is responsible for endothelial dysfunction in several cardiovascular diseases and is associated with severity of disease (12, 36, 44). IR is very frequent in chronic liver disorders and has been associated with the development of hyperglycemia, hepatic steatosis, and enhanced structural damage favoring the occurrence of cirrhosis (32).

Nevertheless, up to now, the prevalence of IR in patients with cirrhosis and the real impact on the pathophysiology of PH have not been adequately evaluated. A recent published clinical study has suggested that the presence of IR, assessed by the HOMA index, could play a role per se in the pathogenesis of PH in patients with cirrhosis with mild hepatocellular insufficiency (Child-Pugh A) (11). Authors from this study suggest that a HOMA value ≥3.5, combined with a low platelet count-to-spleen diameter ratio, could identify those patients with cirrhosis and EV. These two parameters have been validated positively in another independent cohort of 340 patients with cirrhosis. Moreover, there was a positive correlation with the HOMA score and worsening of the hepatic function (33). However, these affirmations have not been accompanied by a hepatic hemodynamic study.

The cohort of patients included in the present study was selected to obtain a homogeneous group and avoid possible confounding factors, which may influence the HOMA-2 index (by altering insulin and glucose levels), such as stress situations, metabolic syndrome, or medically treated diabetes, and its interpretation in cirrhosis.

The present study confirms that IR, assessed by HOMA-2 index, is a very frequent phenomenon in patients with cirrhosis and PH. Indeed, IR was found in ≥60% of our patients, a figure that increased to >70%, if only patients with CSPH were considered. A weak but significant correlation between HOMA-2 index and HVPG was observed. In addition, HOMA-2 index, together with prothrombin time, were the only independent predictors for the presence of CSPH. These findings suggest that IR may play a role in the progression of the chronic liver disease at the earlier stages, as it has already been suggested in patients with nonalcoholic fatty liver disease (16), where the presence of IR was associated with the presence of mild PH (in that study, all patients had HVPG < 10 mmHg). Interestingly, our data, including patients with more severe PH, show that, once CSPH has developed, the correlation between HOMA-2 index and HVPG is lost. These results suggest that, once CSPH has developed, further increments of HOMA-2
index may reflect hyperinsulinism secondary to two different mechanisms: either \( \beta \)-pancreatic hypersecretory state, as suggested by the moderately higher C-peptide levels in patients with IR, or reduction of insulin clearance as a consequence of portal-systemic shunting, as suggested by the observed inverse correlation between HOMA-2 index and C-peptide-to-insulin molar ratio. Indeed, it has been previously shown (7) that, in patients with portal-systemic collateral circulation, the hepatic first pass clearance of insulin decreases and, as a consequence, C-peptide-to-insulin molar ratio decreases, while HOMA-2 index increases. Lack of correlation between HOMA-2 index and NO and Ag vWF levels, as indicators of endothelial dysfunction, does not support a role for IR in the pathophysiology of PH either. These results are consistent with the findings of a previous study (20), which did not find a correlation between peripheral vein insulin concentration and portal pressure in a group of patients with alcoholic cirrhosis and PH.

Overall, from a pathophysiological point of view, the results of our study suggest that IR might have a role in the initial steps contributing to the development of CSPH. But once CSPH has developed, increments of HOMA-2 index may be more a consequence of the unpredictable development of portal-collateral circulation than a cause for the worsening of the severity of PH.

Additionally, our study confirms previous observations demonstrating that EV are more frequent in patients with IR than in those without. However, multivariate analysis disclosed HVPG, either as a continuous variable, or categorized as CSPH vs. non-CSPH, as the only significant variable predicting the presence of gastroesophageal varices. These results clearly demonstrate that an increased HVPG \( \geq \) 10 mmHg, and not IR, is the pathophysiological factor linked to the presence of EV. However, these results strongly suggest that IR may be used as a noninvasive marker of CSPH, an issue that requires confirmation.

Our study also shows that IR does not influence the hemodynamic response to acute intravenous propranolol administration. The effect of propranolol administration on HVPG and systemic hemodynamics was similar for patients with or without IR, and no cutoff value of HOMA-2 was identified to predict the response to intravenous propranolol.

In conclusion, nondiabetic patients diagnosed with liver cirrhosis and CSPH have increased HOMA-2 index. This increment is probably due more to the development of portal-collateral circulation than an impairment of PH secondary to endothelial intrahepatic dysfunction by IR. However, HOMA-2 index may have potential for the noninvasive prediction of CSPH and as a consequence of gastroesophageal varices.

ACKNOWLEDGMENTS

This work has been done as part of a PhD degree in Medicine of E. Erice, at the Universitat Autònoma de Barcelona, Spain.

GRANTS

This study was supported by grants from the Ministerio de Educación e Innovación (SAF2010/7043 to J. C. Garcia-Pagan) and from Instituto de Salud Carlos III (PS 09/01261 to J. Bosch and FIS 08/0193 to J. G. Abrañades) and cofinanced by FEDER funds (EU, “Una manera de hacer Europa”). Ciberehd is funded by Instituto de Salud Carlos III.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


