Association between insulin resistance, metabolic syndrome, and duration of hepatitis C in Egyptian patients

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\textbf{Background}

Chronic hepatitis C virus (HCV) infection affects around 170 million individuals worldwide. Egypt has one of the highest prevalence of patients with HCV worldwide. A higher prevalence of insulin resistance (IR) is found in this population.

\textbf{Aim}

The aim of this study was to assess the relation between IR, metabolic syndrome (MS), and hepatitis C in nondiabetic patients and to assess their relation to the duration of HCV infection.

\textbf{Patients and methods}

This was a cross-sectional study of 50 participants matched for age (49 ± 7.6 years), sex, and BMI. These participants were divided into three groups: 20 controls, 15 patients with HCV for less than 10 years’ duration, and 15 patients with HCV for more than 10 years. We assessed patients for MS according to the AACE diagnostic criteria. Fasting and postprandial insulin levels were also assessed. IR was evaluated using the homeostasis model assessment-insulin resistance (HOMA-IR) equation.

\textbf{Results}

There was a statistically significant difference in HOMA-IR levels between controls (median 0.43 μU/ml) and those with HCV for more than 10 years (median 0.75 μU/ml; \( P = 0.001 \)) as well as those with HCV for less than 10 years (median 0.89 μU/ml; \( P = 0.001 \)). There was no significant difference in HOMA-IR levels between both groups of HCV (\( P = 0.8 \)). The increase in the HOMA-IR test values was mainly because of increased fasting insulin levels in both groups because of the significant positive correlation between HOMA-IR and fasting insulin in patients with chronic HCV less than and those more 10 years’ duration (\( r = 0.902, \ r = 1, \) respectively; \( P = 0.001 \) in both groups). MS was found in four of 15 patients in each group of patients; yet, none of the controls fulfilled the diagnosis criteria.

\textbf{Conclusion}

MS and IR are significantly higher in Egyptian HCV patients when compared with normal controls irrespective of the duration of HCV.

\textbf{Keywords:}

hepatitis C virus, homeostasis model assessment-insulin resistance, insulin resistance, metabolic syndrome

In fact, HCV liver disease and type 2 diabetes mellitus are two already prevalent diseases that will continue to increase in the next decades [3].

CHC has emerged as a complex multifaceted disease with manifestations extending beyond the liver. Hepatic steatosis, insulin resistance (IR), and type 2 diabetes mellitus have been observed to occur more frequently in association with HCV infection than other chronic inflammatory liver diseases [4]. This raises the intriguing question of whether the increase in the prevalence of HCV infection is contributing toward the increasing prevalence of type 2 diabetes mellitus.

An increase in fasting insulin and a higher IR has been observed in HCV-infected patients with a moderate or a severe degree of hepatic fibrosis. In the
Atherosclerosis Risk in Communities Study, a 9-year follow-up showed that antecedent HCV infection was a significant risk factor for developing diabetes in patients with advanced age or high BMI [5].

Romero [4] reported that IR has been associated with the development of steatosis and progression of fibrosis in a genotype-dependent manner.

Furthermore, the initial mechanisms involved in the development of diabetes in HCV infection are under evaluation. There is current evidence that even nondiabetic HCV-infected patients have higher IR than patients with other chronic liver diseases. A chronic inflammatory state could be the missing link. This is supported by elevated tumor necrosis factor-α and interleukin-6 levels in such patients [3].

**Aim**

Our work studies the association between IR and CHC infection in Egyptian patients with a predominant genotype 4 prevalence, as well as the relation between the HCV duration (> or <10 years’ duration) and the presence of IR.

**Patients and methods**

This is a cross-sectional study of 50 patients carried out at the Internal Medicine Department of Kasr El Ainy University Hospital, Cairo. They were classified into the following three groups:

1. **Group A**: It included 15 patients with CHC infection for less than 10 years’ duration.
2. **Group B**: It included 15 patients with CHC infection for more than 10 years’ duration.
3. **Control group**: It included 20 apparently normal individuals. All participants included in this group were seronegative for anti-HCV, HBsAg, HBcAb, IgG, and IgM, and did not have diabetes mellitus.

The duration of hepatitis C was suggested by the date of first transfusion of blood products, intravenous drug use, or a single specific and convincing parenteral exposure, for example, needle stick injury.

**Inclusion criteria**

HCV infection was diagnosed if patients were seropositive for anti-HCV. Confirmation was made by HCV RNA assessment. Chronicity was diagnosed by the presence of HCV antibodies on more than one occasion over a 6-month interval with or without the presence of abnormal liver enzymes.

**Exclusion criteria**

All the studied participants were not known to have diabetes mellitus or hepatitis B infection determined by HBsAg, HBcAb, IgG, and IgM.

All participants were subjected to the following:

1. Full assessment of medical history and a thorough medical examination, including blood pressure measurements.
2. BMI was calculated as weight/height in meters squared (kg/m²).
3. Laboratory investigations included complete blood analysis, urine analysis, fasting and postprandial blood sugar levels, glycosylated hemoglobin levels, fasting and postprandial insulin levels [6], ALT, AST, serum albumin, bilirubin levels, prothrombin time and concentration, blood urea and serum creatinine, lipid profile including total cholesterol, triglycerides, and high-density lipoprotein and low-density lipoprotein cholesterol. HCV antibodies were assessed using the ELISA technique. HCV was assessed by RNA quantitatively and liver biopsy in indicated cases.

Data were analyzed using the SPSS version 10 software (SPSS Inc., Chicago, Illinois, USA).

The homeostasis model assessment-insulin resistance (HOMA-IR) model used for calculation of IR was determined as follows:

\[
\text{HOMA-IR} = \frac{\text{fasting insulin (μU/ml)} \times \text{fasting blood glucose (mmol/l)}}{22.5}
\]

The diagnosis of metabolic syndrome (MS) was made according to the American Association of Clinical Endocrinology (AACE) as follows: Any three or more of the following: BMI 25 kg/m² or more, blood pressure 130/85 mmHg or more, fasting glucose level more than 110–126 mg/dl, 2 h postprandial glucose level more than 140 mg/dl or more, high-density lipoprotein less than 40 mg/dl in men and less than 50 mg/dl in women.

**Results**

Table 1 shows the fasting insulin levels in the different study groups expressed in median values. Fasting insulin in patients with CHC for less than 10 years’ duration had a median of 4.46 μU/ml (range 2.42–10.28 μU/ml), whereas postprandial levels had a median of 9.32 μU/ml (range 2.4–300 μU/ml) compared with the controls, with a median of 2.86 μU/ml (range 2.14–5.09 μU/ml) in the fasting state \((P < 0.001)\) and 4.16 μU/ml (range 2.67–6.09 μU/ml) in the postprandial state \((P < 0.001)\). Fasting insulin in CHC for more than 10 years’
duration had a median of 3.38 μU/ml (range 2.51–47.56 μU/ml) and a postprandial median of 9.15 μU/ml (range 2.48–30.4 μU/ml). The P value was 0.043 and 0.016, respectively, when compared with the controls. However, there was no statistical difference between the two CHC groups in the fasting (P = 0.48) and postprandial insulin levels (P = 0.46).

The HOMA-IR showed similar results, with a significant difference between controls and the two HCV groups; yet, there were no significant differences between the two groups of HCV with different durations of disease. This is shown in Table 2.

Table 1 Measurement of serum insulin levels (μU/ml) both in the fasting and in the postprandial states among the groups studied

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CHC &lt; 10 years</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting insulin level (μU/ml)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Median</td>
<td>2.86</td>
<td>4.46</td>
<td>0.001</td>
</tr>
<tr>
<td>Range</td>
<td>2.14–5.09</td>
<td>2.42–10.28</td>
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<tr>
<td>2 h postprandial insulin level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4.16</td>
<td>9.32</td>
<td>0.001</td>
</tr>
<tr>
<td>Range</td>
<td>2.67–6.09</td>
<td>2.44–100</td>
<td></td>
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</table>

Fasting insulin level
<table>
<thead>
<tr>
<th>Control</th>
<th>CHC&gt;10 years</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>2.86</td>
<td>3.38</td>
</tr>
<tr>
<td>Range</td>
<td>2.41–5.09</td>
<td>2.51–47.56</td>
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<tr>
<td>2 h postprandial insulin level</td>
<td></td>
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<tr>
<td>Median</td>
<td>4.16</td>
<td>9.15</td>
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<tr>
<td>Range</td>
<td>2.67–6.09</td>
<td>2.48–30.40</td>
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CHC, chronic hepatitis C. P < 0.05, significant.

Table 2 Homeostasis model assessment-insulin resistance among the groups studied

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CHC &lt; 10 years</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>HOMA-IR test</td>
<td></td>
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<td></td>
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<tr>
<td>Median</td>
<td>0.43</td>
<td>0.89</td>
<td>0.001</td>
</tr>
<tr>
<td>Range</td>
<td>0.24–0.83</td>
<td>0.42–1.97</td>
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<tr>
<td>CHC&lt;10 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.43</td>
<td>0.75</td>
<td>0.001</td>
</tr>
<tr>
<td>Range</td>
<td>0.24–0.83</td>
<td>0.43–12.72</td>
<td></td>
</tr>
<tr>
<td>CHC&gt;10 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.89</td>
<td>0.75</td>
<td>0.806</td>
</tr>
<tr>
<td>Range</td>
<td>0.42–1.97</td>
<td>0.43–12.72</td>
<td></td>
</tr>
</tbody>
</table>

CHC, chronic hepatitis C; HOMA-IR, homeostasis model assessment-insulin resistance. P < 0.05, significant.

Table 3 shows the correlation between HOMA-IR and levels of insulin and glucose in both groups of CHC patients.

Table 4 shows the classification of the different groups studied according to the MS criteria.

Discussion

Despite the fact that the definitions of MS differ in detail and cut-off levels for several components of the MS, they agree on the following central traits: Obesity, disturbed glucose homeostasis, dyslipidemia, and hypertension. HCV is now considered a systemic disease involving lipid metabolism, oxidative stress, and mitochondrial function [7]. The relationship between HCV and type 2 diabetes mellitus and or IR has been the focus of many studies.

Age, sex, and BMI are risk factors for IR. All our patients and controls were age, sex, and BMI matched. Our study found a significantly higher fasting serum insulin level in CHC groups than in the control group. However, differences between levels of fasting serum insulin in CHC patients less than 10 years’ duration and those more than 10 years were not statistically significant. HOMA-IR levels did not differ significantly between the two HCV groups, suggesting that IR presents earlier than 10 years. The fasting serum glucose levels were also increased in both groups of CHC when compared with those of the control group, but still below the levels needed to diagnose diabetes.
These results were in agreement with those of Hui et al. [8], who reported that HCV patients without a history of diabetes mellitus had significantly higher levels of all markers of IR, including fasting glucose, fasting serum insulin, C peptide, and HOMA-IR, compared with healthy volunteers. Furthermore, Lecube et al. [3] reported an increased IR in HCV-infected patients with a moderate or a severe degree of fibrosis. Even HCV-infected patients without hepatic fibrosis presented with higher IR than patients with primary biliary cirrhosis with different degrees of fibrosis. These data are in agreement with our results showing no association between IR in HCV patients and HCV duration, that is, development of fibrosis.

In our study, the HOMA-IR test values correlated positively with insulin and glucose levels. The increase in the HOMA-IR test values was mainly induced by an increase in fasting serum insulin levels.

This was evident in both CHC groups. This may relate to the lack of destruction of insulin by the liver cells rather than an increase in pancreatic insulin production.

Custro et al. [10] reported an incidence of diabetes mellitus in adults with HCV four times higher than the general population. Moucari et al. [7] reported a 32.4% of IR in nondiabetic CHC patients. Some indicate an independent coexistence, whereas others confirm an association in the presence of confounding factors.

Imazeki et al. [11] has shown that viral eradication after antiviral treatment can lead to cure of type 2 diabetes mellitus. This offers a strong argument in favor of a causal relationship. Furthermore, HCV-dependent upregulation of SOC-3 transcription factor may be responsible for induction of cell resistance toward insulin [12]. Also, an Egyptian study showed an elevation in interleukin-1 in HCV patients, which could be an additional link in the causal relationship [13].

To support this view, the increase in the HOMA-IR test values in both HCV groups was mainly because of increased fasting insulin levels in both groups, irrespective of whether it was more or less than 10 years’ duration. This suggests that irrespective of the underlying possible correlating mechanisms, they involve hyperinsulinemia. In addition, elevation in insulin levels start relatively earlier than 10 years. Another common link in the development of IR and liver disease in the form of steatosis is the adipocyte-secreted proteins leptin and adiponectin. Patel et al. [14] observed that leptin levels are elevated in NASH and CHC infection. Moreover, leptin levels correlated independently with hepatic steatosis and increased leptin expression in hepatocytes attenuated several insulin-induced activities including tyrosine phosphorylation.

Interestingly, a recent Egyptian study showed IR to be an important determinant of sustained viral response in genotype 4 CHC patients, a strain highly prevalent in Egyptian patients, adding further evidence to the link between the two conditions [9].

We found a blood pressure elevation of more than 130/85 mmHg in CHC patients than in the control groups. Hypertension was present in 26 and 40% of the patients in the CHC group less than 10 years and those more than 10 years, respectively.

IR is considered to be an important pathogenic mechanism in essential hypertension. A number of studies have been consistent in showing that IR is associated with higher blood pressure in nondiabetic individuals [14,15]. In our study, the MS was diagnosed in 26% of CHC patients more than 10 years’ duration and 26% of CHC patients less than 10 years’ duration. None of the controls in the study fulfilled the three criteria for the MS.

**Conclusion**

In conclusion, our study provides evidence that CHC infection is associated significantly with IR in Egyptian patients irrespective of the duration of the HC infection, whether longer or shorter than 10 years. Hyperinsulinemia was the main presenting feature. Other features of MS presented in 26% of both groups of CHC patients; yet, they were not found in the control group. In the future, HCV infection needs to be considered not only as a liver disease but also as part of a metabolic disease. Early monitoring and treatment of hyperglycemia is recommended in patients with HCV infection.

**Acknowledgements**

There are no conflicts of interest.

**References**