Effect of HCV on fasting glucose, fasting insulin and peripheral insulin resistance in first 5 years of infection

Naeema Ahmed, Amir Rashid, Abdul Khaliq Naveed, Qudsia Bashir

Abstract
Objective: To assess the effects of hepatitis C virus infection in the first 5 years on fasting glucose, fasting insulin and peripheral insulin resistance.

Methods: The case-control study was conducted at the Army Medical College, Rawalpindi, from December 2011 to November 2012, and comprised subjects recruited from a government hospital in Rawalpindi. The subjects included known cases of hepatitis C virus infection for at least 5 years, and normal healthy controls. Fasting blood samples of all the subjects were collected and analysed for serum fasting insulin and serum fasting glucose levels. Homeostatic model assessment-Insulin resistance was calculated SPSS 11 was used for statistical analysis.

Results: Of the 30 subjects, 20(66.6%) were cases, while 10(33.3%) were controls. Serum fasting glucose mean level in cases was 89.55±9.53 compared to 84.40±9.80 in the controls (p=0.188). The mean serum fasting insulin in controls was 7.52±3.23 and 6.79±3.30 in cases (p=0.567). Homeostatic model assessment-Insulin resistance level in controls was 1.60±0.76 and in the cases it was 1.49±0.74 (p=0.695).

Conclusion: Peripheral insulin resistance and development of type 2 diabetes as a complication of hepatitis C virus infection was not likely at least within the first five years of infection.

Keywords: Hepatitis C Virus (HCV), Peripheral insulin resistance (IR), Type2 diabetes mellitus (T2DM), Homeostatic model assessment-insulin resistance (HOMA-IR).

Introduction
Hepatitis is a disease that has been with us for a long time. It has been discussed in the literature as far back as in Hippocrates' writings. The hepatitis C virus (HCV) was discovered in 1989, from chimpanzees infected with a non-A-non-B agent and shortly thereafter, serological assays to detect HCV were developed. HCV is one of the major causes of chronic liver disease, cirrhosis and liver cancer. It is a worldwide epidemic affecting over 180 million individuals. Moreover, 3-4 million individuals are newly infected each year with HCV and about 10% of the Pakistani population has been infected so far. Much controversy exists regarding the natural history of HCV. It belongs to the genus Hepacivirus within the Flaviviridae family. HCV infection is often silent and progresses slowly. A possible association has been found between chronic hepatitis C (CHC) and glucose levels. A relationship between HCV and insulin resistance (IR) has been highlighted in adult population. IR is defined as a condition in which higher insulin concentrations are needed to achieve normal glucose metabolism or in which normal insulin concentrations fail to achieve normal glucose metabolism. The gold standard technique for IR assessment is the euglycaemic hyperinsulinaemic clamp. However, another accepted method for the assessment of systemic IR is the Homeostatic model assessment-Insulin resistance (HOMA-IR). No method has been established for the measurement of insulin responsiveness of the liver, pancreas, muscle or fat. HOMA-IR is calculated as follows:

\[
\text{Fasting Glucose (mmol/l) x Fasting Insulin (mIU/l)} \div 22.5
\]

A better understanding of the mechanisms underlying IR in CHC is required for the development of treatment of IR and it should be aimed at the prevention of progression of fibrosis and for the achievement of sustained virological response (SVR).

Mechanism of development of IR and its complications is still not clear. Evidence showed that impaired insulin signalling is seen in the cells possessing HCV proteins. Defects at any level in the insulin signalling pathway can result in IR. All types of HCV genotypes have been associated to a different extent with IR. It has been shown that genotype 3a affects the insulin signalling
pathway through down-regulation of peroxisome proliferator-activated receptor.\textsuperscript{10} It has been shown that there is increased production of suppressor of cytokine signalling 7 (SOCS 7) in genotype 3, resulting in diminished insulin receptor substrate 1 (IRS-1) and thus leading to IR.\textsuperscript{11} IRS-1 is down-regulated by mammalian target of Rapamycin (mTOR) in genotype 1b which shows a connection between HCV-1b infection and IR at the early stage of liver disease.\textsuperscript{12} IR and development of type 2 diabetes mellitus (T2DM) has been shown to be associated with progression of liver fibrosis.\textsuperscript{13} So, it is not usually encountered in early years of HCV infection.

The current study was planned to assess the effects of HCV infection in the first 5 years on fasting glucose, fasting insulin and peripheral IR.

\textbf{Patients and Methods}

The case-control study was conducted at the Centre for research in Experimental & Applied Medicine (CREAM), Department of Biochemistry and Molecular Biology, Army Medical College, Rawalpindi, from December 2011 to November 2012, and comprised subjects recruited from a government hospital in Rawalpindi. After getting approval from the institutional ethical committee, known cases of HCV infection for last 5 years were registered, while normal healthy subjects were taken in as controls. Already diagnosed cases of T2DM, patients with any liver disease other than hepatitis C and patients with any diagnosed pancreatic disease were excluded. After written informed consent from all the subjects, blood samples were collected and analysed for serum fasting insulin (Access II immunoassay) and serum fasting glucose levels (Enzymatic Colorimetric Method). For fasting glucose, the samples were prepared according to the kit manual instructions and they were run on auto-analyser Selectra E (The Netherland). Serum fasting glucose was measured in mmol/L. Reference values for serum fasting glucose were 3.89-5.83 mmol/L. Serum fasting insulin was calculated by processing the samples through Access 2 immunoassay system. It was measured in \( \mu \text{IU/ml} \) with the reference values ranging from 2 - 25 \( \mu \text{IU/ml} \).

HOMA-IR was calculated as per the standard formula.\textsuperscript{7}

Data was analysed using SPSS 11. Mean and standard deviation was calculated for age and gender. Level of significance was set at \( p \leq 0.05 \).

\textbf{Results}

Of the 30 subjects, 20(66.6\%) were cases, while 10(33.3\%) were controls. Overall, there were 17(57\%) men (Table-1).

The mean age of the cases was 39.80±8.18 years (range: 29-59 years), while that of the controls was 37±4.92 years (range: 33-45 years) (\( p=0.188 \)) (Table-2).

Serum fasting glucose in the cases was 89.55±9.53 compared to 84.40±9.80 in the controls. Mean serum fasting insulin in controls was 7.52±3.23 and 6.79±3.30 in the cases (\( p=0.567 \)).

Similarly, HOMA-IR level in controls was 1.60±0.76 and 1.49±0.74 in the cases (\( p=0.695 \)) (Table-3).

\begin{table}[h]
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\begin{tabular}{llll}
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\textbf{Parameters} & \textbf{Group} & \textbf{N} & \textbf{Mean} & \textbf{Std. Deviation} & \textbf{P-Value} \\
\hline
Serum Fasting Glucose (mg/dl) & HCV Infected patient & 20 & 89.55 & 9.53 & 0.188 \\
& Controls & 10 & 84.40 & 9.80 & \\
Serum Fasting insulin (\( \mu \text{IU/ml} \)) & HCV Infected patient & 20 & 6.79 & 3.30 & 0.567 \\
& Controls & 10 & 7.52 & 3.23 & \\
HOMA-IR & HCV Infected patient & 20 & 1.49 & 0.74 & 0.695 \\
& Controls & 10 & 1.60 & 0.76 & \\
\hline
\end{tabular}
\caption{Comparison of serum fasting glucose, serum fasting insulin and HOMA-IR in HCV infected patients and controls.}
\end{table}

HCV: Hepatitis C virus.

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Discussion

Chronic viral hepatitis is a major health problem caused by hepatitis B virus (HBV) or HCV. Several studies have shown that HCV is associated with increased incidence of T2DM. Development of HCV-induced IR is a highly complex mechanism that is still not clear as IR is limited to the organs or tissues that are infected by HCV. IR is one of the major risk factors for the development of T2DM. HCV doesn’t induce T2DM and IR early in the course of the illness. There is an association of HCV with hepatic steatosis which further leads to IR and T2DM. In our study, HOMA-IR remained the same in both the cases and the controls. This showed the absence of peripheral IR. Thus, there was no hepatic as well as peripheral IR. Similar results were seen in a study which found no correlation between hepatic IR and peripheral IR when infected with HCV. Another study showed normal HOMA-IR levels in children with CHC and controls. This study may appear contradictory with our findings as it was not carried out in adult population. Another study is in concordance with our findings and showed that there was no increase in HOMA-IR levels in HCV infection, but there was a significant increase in HOMA-IR levels in patients with significant fibrosis. A study was against our findings, showing a strong correlation between CHC, increase in peripheral IR and HOMA-IR values. However, there was no time limit regarding duration of diagnosis of HCV infection in that study.

In another study, HOMA-IR values were highest in non-diabetic patients with CHC compared to the control group. Another study compared the levels of fasting serum insulin, C peptide and HOMA-IR, and found a significant increase in all parameters. This association of CHC with IR was subsequently confirmed in further studies. In the above studies, duration of HCV infection was not taken into consideration.

Conclusion

Though peripheral IR and T2DM are known complications of HCV infection, they are not likely to occur at least within the first five years of infection. Early detection and management of HCV infection is likely to avoid the development of IR and T2DM.

References