COULD HEPATITIS C VIRUS AFFECT THE PANCREATIC FUNCTIONS?

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ABSTRACT

The association between Hepatitis C virus (HCV) and diabetes mellitus remains undetermined and must be defined. So, the aim of this work was to study serum insulin, C-peptide and amylase concentrations in patients with chronic hepatitis C virus (CHCV) infection in a trial to search for any pathogenic impact of HCV on both the endocrine and exocrine functions of the pancreatic gland. This work was carried on 75 patients and 20 healthy subjects as controls. All our patients and controls were males and their ages ranged from 40 to 64 years. Patients were classified into diabetic, CHCV, and diabetic with CHCV groups. Each group included 25 males.

The results of this work showed a significant increase of S. glucose in diabetics, with and without CHCV ($p < 0.001$) while liver enzymes (AST & ALT) were significantly increased in CHCV with and without DM ($p < 0.001$) compared with the control group.

Additionally, diabetic group showed a significant increase of S. insulin & C-peptide ($p < 0.05$) while CHCV group showed a significant

increase of S. amylase ($p < 0.001$) compared with the control group. Diabetics with CHCV showed a significant decrease of both serum insulin & C-peptide ($p < 0.05$) but a significant increase of S. amylase ($p < 0.001$) compared with the control group.

Comparative study of diabetic with CHCV group versus diabetic group and CHCV group, the data showed a significant decrease of S. insulin and C-peptide ($P_1 < 0.001$ & $p_2 < 0,05$), respectively while S. amylase was significantly increased comparing it with DM group, ($pi < 0.001$) but non-significant change did not occur when compared with CHCV group ($P_2 > 0.05$).

We could conclude that; both the exocrine and endocrine parts of the pancreas may be an extrahepatic target of HCV. The disturbances of both insulin & C-peptide associated with CHCV could explain a direct link between HCV and occurrence of diabetes mellitus. So, we recommend to assay S. glucose, insulin & C - peptide levels in every patients with CHCV to predict the incidence of diabetes mellitus.

INTRODUCTION AND AIM OF THE WORK

Hepatitis C virus (HCV) is a major public health problem nowadays. About 50% of acute HCV infection becomes chronic (Paver and Turner, 1993).

Infection with HCV may have effects not only on the liver but also, on various extrahepatic tissues (Gumber and Chopra, 1995).

Hepatitis C and diabetes mellitus (DM) represent an ongoing controversy (Zein, 1998). While Ozyilkan and Arslan (1996) and Grimbert et al. (1996) reported a high prevalence of DM in patients with chronic hepatitis C virus (CHCV), Mangia et al. (1998) disproved HCV infection as a triggering factor for DM.

Similarly, the association between HCV infection and elevated serum amylase concentrations (Hyperamylasemia) is controversial (Pezzilli et al, 1999). Hyperamylasemia is frequently found in patients with CHCV comparing with the normal subjects (Simsek et al., 1996). On the other hand, Tsianos et al. (1996) did not find hyperamylasemia in patients with CHCV.

So, the aim of this work is to evaluate serum insulin, C-peptide and amylase concentrations in patients with chronic hepatitis C virus in a trial to search for any pathogenic impact of HCV on both the endocrine and exocrine functions of the pancreatic gland.

PATIENTS AND METHODS

Ninty-five male subjects were included in this study. Their ages ranged from 40 to 64 years. They were selected from outpatients clinics of diabetes mellitus and hepatology, Benha University Hospital. The patients and control subjects were matched together for sex, age and body mass index (BMI). They were divided into four groups :

- ***Group I*:** They were formed of 20 male, healthy subjects as controls.
- ***Group II*** *:* They were formed of 25 male patients with type II D.M. The duration of DM ranged from 6 to 21 years with the mean value (13 ± 0.7). They were controlled with diet regimen and oral hypoglycaemic drugs.
- ***Group III :*** They were formed of 25 male patients with CHCV. The duration of HCV contamination ranged from 3 to 10 years with the mean value (6 ± 0.4).
- ***Group IV*:** They were formed of 25 male patients with both DM and CHCV. The duration of DM ranged from 6 to 22 years with the mean value (12 ± 0.9). They were controlled with diet regimen and oral

hypoglycaemic drugs. The duration of HCV contamination ranged from 5 to 15 years with the mean value (9 ± 0.65).

For all subjects the fallowings were done:

1- Full history taking & clinical examination.
2- Abdominal ultrasonography.
3- Body mass index as an index of obesity (kg/m^2) (National diabetes data group, 1979).
4- Liver biopsies were done by percutaneous technique for all HCV-seropositive patients with positive HCV-RNA.
5- Sampling:

A morning sample of 5ml venous blood was drawn after an overnight fasting, from all subjects. The samples were divided into 2 parts. The first part was put in a sterile centrifuge tube. The separated sera were used for determination of:

- Hepatitis B surface antigen by ELISA (Bonilo and Dovis, 1982)
- HCV antibody (Choo et al., 1989).
- HCV antigen by PCR (Ali and Jameel, 1993)

The second part was centrifuged and the sera separated were used for determination of:

- Fasting serum glucose. (Trinder, 1969).
- Serum total bilirubin. (Pearlman & Lee, 1974).
- Serum alanine transferase (ALT). (Reitman and Frankel. 1957).
- Serum aspartate transferase (AST). (Reitman and Frankel. 1957).
- Serum albumin (Grant and Kachmar, 1970).
- Serum creatinine. (Henry, 1974).

The remaining parts of the sera were kept frozen at - 80°C until assay of:

- Serum insulin by radio-immuno assay (RIA) (Robinson et al., 1996).

- **Serum C-Peptide by RIA (Ta - Jen et al.? 1995).**
- **Serum amylase by kinetic method. (Junge et al., 1997).**

Diagnosis of chronic hepatitis C virus was based on the presence of positive HCV antibody by RIB A II and confirmed by positive HCV antigen by PCR and liver biopsy showing stigmata of chronic hepatitis (Sherlock, 1992).

Diagnosis of diabetes mellitus was based on a history of receiving oral hypoglycaemic drugs or fasting serum glucose more than 126 mg/'dl on more than one occasion in the absence of a specialized diet or parenteral nutrition (The Expert Committee on Diagnosis and Classification of Diabetes Mellitus, 1997).

***Exclusion Criteria*:**

Patients with hepatitis B-Virus infection.

Liver cirrhosis or decompensated liver disease (ascitis, Jaundice, encephlopathy, portal hypertension).

Patients with renal, salivary gland, biliary tract, malignant, genetic and other endocrine disorders.

Patients with a history of alcohol or any drug intake specially interferone - a (IFN - a).

RESULTS

The diabetic group showed a significant increase of fasting S. glucose, insulin and C-peptide ($p < 0.05$) while, there were non-significant increase of S.ALT, AST and amylase compared with the control group.

- **The CHCV group : showed a significant increase of S.ALT, AST and amylase ($p < 0.001$) while, there were non - significant changes of fasting S.glucose, insulin & C-peptide compared with the control group.**
- **The diabetic with CHCV group; showed a significant increase of fasting S.glucose, ALT, AST and amylase ($p < 0.001$) while, there were significant decrease of S.insulin and C-peptide ($p < 0.05$) compared with the control group.**
- **Comparative study of diabetic with CHCV group versus DM group and CHCV groups : the results revealed that significant changes of fasting S.glucose, ALT, AST, insulin, C-Peptide and amylase ($pi < 0.001$) when compared with the diabetic group. There were non-significant increase of AST and amylase while fasting S.glucose ($p2 < 0.001$), ALT, insulin and C-peptide were significantly changed ($p_2 < 0.05$) in diabetic with CHCV group when compared with CHCV group.**

The data were tabulated as mean, ± SE and statistically analyzed using student (t) test. P values less than 0.05 were consideced significant.

Table (I) : Mean values and ± SE of some routine investfgations in different groups compared with each others.

Biochemical pirameters / Studied group5	Fasting serum glucose (mg/dl)	S.ALT (U/L)	S.AST (U/L)
Control group (n = 20)	**92.5 ± 1.36**	**8.1 ±0.50**	**7.8 ±0.36**
Diabetic group (n = 25)	**160 ±6.3 p< 0.001**	**9±0.31 p > 0.05**	**8 ± 0.29 p>0.05**
CHCV group (n = 25)	**95 ±1.23 p > 0.05**	**138 ±2.38 p< 0.001**	**110 ±3.04 p< 0.001**
Diabetic with CHCV group (n = 25)	**188 + 4.3 p< 0.001 Pi < 0.001 P_2< 0.001**	**148 ±2.92 p< 0.001 Pi < 0.001 P_2 < 0.05**	**112 ±2.67 p< 0.001 p, < 0.001 P_2 > 0.05**

p : Probability versus control group,
p_1 : Probability versus D.M group.
p_2: Probability versus CHCV group.

Table (2) : Mean values and ± SE of S. insulin, C-peptide and amylase in all studied groups compared with each others.

Biochemical parameters / Studied groups	S. insulin (ulU/ml)	S.C-peptide (ng/ml)	S. amylase (U/L)
Control group (n = 20)	9.85 ±0.58	1.34 ±0.07	51.9 ±2.85
Diabetic group (n = 25)	12 ±0.7 p < 0.05	1.64 ±0.08 p < 0.05	54 ±2.50 p > 0.05
CHCV group (n = 25)	9 ±0.5 p > 0.05	1.22 ±0.06 p > 0.05	76 ±4.1 p< 0.001
Diabetic with CHCV group (n = 25)	7 ±0.6 p < 0.05 P_I < 0.001 p_2<0.05	1.04 ±0.06 p < 0.05 Pi < 0.001 P_2<0.05	78 ±4.8 p< 0.001 p, < 0.001 p_2>0.05

P : Probability versus control group.
P_1 : Probability versus D.M group.
p_2 : Probability versus CHCV group.

DISCUSSION

HCV is a major health problem nowadays. About 50% of patients with acute disease develop chronic hepatitis (Paver & Turner, 1993).

A surprisingly high percentage of the Egyptian are seropositive for HCV antibodies. In a large survey study including 4000 subjects, the rate of HCV seropositivity was 9% (Kabil et al., 1995).

HCV and diabetes mellitus represent an ongoing controversy (Zein, 1998). In the same way, the association of HCV infection and hyperamylasemia is controversial (Pezilli et al., 1999).

In this study, the mean values of both serum ALT & AST were and significantly increase in patients with CHCV infection group 3) and diabetic patients with CHCV (group 4) compared with the control. This was in accordance with Frazer et al. (1996).

HCV infection causes damage of hepatocytes with increased permeability of its membrane. Cytosolic isoenzymes as ALT spills into the sinusoids and then into the peripheral blood. Permeability of the mitochondrial membranes also, increase and mitochondrial isoenzymes as AST is released as well (Choo et al., 1991).

This continuous parenchymal damage pointed out to a great risk specially in children following HCV infection (El-Nawawy et al., 1995).

In this work, the mean values of serum ALT and AST were significantly increased in diabetic patients with CHCV (group 4) when compared to those of CHCV (group 3). This was in consistence with Simo et al. (1996). These biochemical changes may be related to some viral

factors as the duration of HCV contamination or HCV genotypes (Frazer et al., 1996).

The present data revealed that, the mean values of both serum insulin and C-peptide were statistically higher in the diabetic group compared with the control group. These data were compatible to the results of Grimbert et aL (1996),

The Hyperinsulinemia and increased C-peptide in type-2 diabetic patient could be the result of insulin resistance, specially in obese patients (Kolterman, et al., 1979). As obese subjects in this study were not excluded.

Both S. insulin & C-peptide were non-significantly decreased in CHCV group compared with the control group. These results were in agreement with Kaneko et al. (1995).

The present results showed that, the mean values of both serum insulin and C-peptide in diabetic with CHCV group were statistically lower than that of the control group ($p < 0.05$). These findings were in consistent with Grimbert et al. (1996).

The first question central to these results would be, whether hypoinsulinemia found in diabetic patients with CHCV were secondary to CHCV infection or were they just an association of two common pathologies?

To answer this question, the following data were obtained on comparing diabetic patients with CHCV versus the diabetic group. We found that diabetic group had hyperinsulinemia while diabetic patients with CHCV group had hypoinsulinemia Several possible hypothetic mechanisms were postulated to clarify the diabetogenic action of HCV. Firstly, immunological hypothesis I serum antoantibodies to nuclei

(ANA), smooth muscles (SMA) and liver-kidney microsome (LKM) occur in one third of patients with CHCV infection (Lenzi et al., 1996). An autoantibody to liver-pancreas antigen was also described as a subgroup of autoimmune hepatitis. This might have a link with HCV infection (Stechemesser et al., 1993). Simo et al. (1996) concluded that an auto-immune destruction of the endocrine part of the pancreatic tissues related to HCV antigen or immunocomplexes could not be excluded.

Secondly, direct cytopathic hypothesis : many viruses had been claimed to infect pancreatic islet cells inducing direct damage of B-ceils (Zein, 1998), examples are congenital rubella (Forrest et al., 1971) Coxsackie-B virus (King et al., 1983), mumps (Karjalainen et al., 1988), hepatotropic viruses as cytomegalovirus (Pack et al., 1988) and hepatitis B virus (Brechot et al., 1984). Similarly HCV could infect pancreatic islets and destruct B-cells (Simo et al., 1996). So, HCV might have a direct role in pancreatic B-Cells destruction.

Thirdly, biochemical hypothesis : HCV infection is associated with an increased prevalence of iron overload (Farigon et al., 1992). The relationship between iron overload and development of DM is most evident in haemochromatosis. The mechanism is likely to be related to damage of the endocrine part of the pancreas by excessive iron deposition (Simo et al., 1996).

Contradictory to these results, Del Olmo et al. (1996) and Mangia et al. (1998) found no significant relation between HCV seropositivity and DM in patients with chronic hepatitis C viral infection (CHCV). In addition, Mangia et al. (1998) found predominant hyperinsulinemia in these patients. Moreover, they stated that the increased prevalence of DM in CHCV patients should be ascribed to the diabetogenic effect of cirrhosis and liver failure themselves and not to HCV. But, in our study,

we exclude patients with cirrhosis & liver cell failure. However, Letiexhe et al. (1993) reported that hyperinsulinaemia in decompensated liver disease may be due to portosystemic shunting and so, insulin clearance by the liver is decreased.

It is possible that HCV infection may serve as an additional risk factor for the development of DM beyond that attributable to chronic liver disease alone (Mason et al., 1999).

In this work, the mean value of S. amylase in CHCV and diabetic with CHCV groups was statistically significant when compared with the control group ($p < 0.001$). This finding was similar to the results of (Ventrucci et al., 1996)

The second question, does hyperamylasemia in CHCV patients denote a coexistant pancreatic insult?. Many hypothesis were formulated in this regard as the presence of circulating amylase-IgG macromolecules in CHCV patients (Sgrabi et al., 1996) or may be due to the direct cytopathic action of HCV on the exocrine part of the pancreatic gland (Simsek et al., 1996) or may be due to observation of Kataev et al. (1993) who found pronounced elevation of serum amylase activity in pancreatic juice.

However, Tsianos et al. (1996) and Pezzilli et al. (1999) explained the hyperamylasemia as due to decrease liver metabolism of amylase in cirrhotic patients leading to its accumulation in the circulation.

Many researchers proved that liver cirrhosis is not a prerequisite for the development of hyperamylasemia in CHCV patients like Taranto et al. (1989) who suggested that a mild pancreatic damage may occur during the acute state of viral hepatitis regardless of the incriminating virus.

A completely opposing suggestion was provided by Caradonna et al. (1996) that the prevalence of pancreatitis and hyperamylasemia were low

in cirrhotic patients. They added that possible cirrhosis with secretion of high volume, low-protein juice confers a protective effect on the pancreas.

We could conclude that, both the exocrine and endocrine parts of the pancreas may be an extrahepatic target of HCV. The disturbances of both insulin & C-peptide associated with CHCV could explain a direct link between HCV and occurrence of DM. So, we recommend to assay serum glucose, insulin and C-peptide levels in every patients with CHCV to predict the incidence of diabetes mellitus.

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