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Multidisciplinary Academic Journal Publisher

Prevalence of Anti-Islet cell antibody in patients with hepatogenous diabetes

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Abstract: Background: Diabetes is frequently found in patients with chronic hepatitis C virus (HCV) infection even before the development of advanced liver disease. The underlying mechanism responsible for derangements in glucose tolerance is poorly understood. **Objective:** To detect the presence of anti-islet cell antibodies in patients with hepatitis C virus and diabetes. **Patients and methods:** The study included 80 subjects, 40 chronic hepatitis C adult patients (18 to 75 years old) of both sexes with positive HCV ribonucleic acid (RNA), not previously subjected to antiviral therapy and having type2 diabetes mellitus, who are attending the outpatient clinic of internal medicine department of Fayoum University Hospital, 40 obese type 2 diabetic patients with negative HCV antibody. A Full medical history was taken from both groups including the patient's age, sex, history of HTN, family history of diabetes. All subjects were subjected to complete physical examination, CBC, liver enzymes, kidney function tests, random blood sugar, HCV antibody, HCV RNA for HCV positive diabetic patients, islet cell antibody, Fib4 for group I and abdominal ultrasound examination. **Results:** There was no statistically significant difference between group I, group II as regards the positivity of internal carotid artery (ICA), the prevalence of positive ICA was 16.3% of total study group, the prevalence of patients with positive ICA in group I is 17.5%, the prevalence of patients with positive ICA in group II is 15%. **Conclusion:** Islet cell antibodies do not appear to play a significant role in the pathophysiology of diabetes in HCV infected patients.
[Mohamed Abdel Hady Mashahit, Hoda Abd El Badie Hussein, Hala Sayed Eltoukhy, Noha Khalifa Abd ELghaffar , Reham Samir Ahmed Seif El Yazel. **Prevalence of Anti-Islet cell antibody in patients with hepatogenous diabetes.** *Nat Sci* 2021;19(6):39-46]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature 7. doi:10.7537/marsnsj190621.07.

Keywords: Anti-Islet cell antibody, Hepatogenous diabetes, HCV, RNA

1. Introduction

Diabetes mellitus is a rapidly-growing worldwide epidemic Approximately 5 million people aged between 20 and 79 years died from diabetes in 2015, equivalent to one death every six seconds **(Ogurtsova et al., 2015).** Chronic hepatitis C (CHC) infection has a global prevalence of 2%-3%. Approximately 170 million people are thought to be currently infected (approximately 3% of the world's population), and an additional 3-4 million are infected each year **(Alter, 2007).** Pooled mean HCV prevalence was estimated at 11.9% among the general population in Egypt **(Kouyoumjian et al., 2018).**

This virus is not only a frequent cause of chronic liver diseases, including hepatitis, cirrhosis, and hepatocellular carcinoma (HCC), but it is also involved in the pathogenesis of various autoimmune and rheumatic disorders (e.g., arthritis, vasculitis, sicca syndrome, porphyria cutanea tarda, lichen planus, nephropathies, and lung fibrosis) and in the development of B-cell lymphoproliferative diseases. Chronic hepatitis C is a multifaceted disorder that is associated with extrahepatic manifestations, including endocrinological disorders, thyroid disorders and diabetes **(Antonelli et al., 2008).**

Diabetes mellitus (DM) that occurs because of chronic liver disease (CLD) is known as hepatogenous diabetes (HD). Although the association of diabetes and liver cirrhosis was described forty years ago, it was scarcely studied for long time. Patients suffering from this condition have low frequency of risk factors of type 2 DM. Its incidence is higher in CLD of viral, alcoholic and cryptogenic etiology **(García-Compeán et al., 2016).**

HCV infected individuals have 3 times increased likelihoods of having DM than the general population. Also, eradication of HCV may produce a remission of diabetes **(Arase et al., 2009).**

Few data on the association between HCV and type 1 DM have been reported, and published studies have shown only small proportions of CHC patients positive for one or more markers of pancreatic autoimmunity **(Antonelli et al., 2014).**

The aim of the present study to detect the presence of anti-islet cell antibodies in patients with hepatitis C virus and diabetes.

2. Patients and methods

This study included 80 individuals, 40 chronic hepatitis C adult patients (18 to 75 years old) of both sexes with positive HCV RNA, not previously subjected to antiviral therapy and having type 2 diabetes mellitus, who are attending the Outpatient Clinic of Internal Medicine Department of Fayoum University Hospital (Group I), and 40 obese type 2 diabetic patients with negative HCV Ab (Group II). The study was conducted from August 2017 to December 2018.

Inclusion criteria:

- Chronic hepatitis C adult patients aged 18 to 75 years old of both sexes with HCV antibody positive by ELISA (enzyme linked immunosorbent assay) and HCV-RNA detected by PCR (Polymerase chain reaction) for at least 6 months.
- Patients who developed type 2 diabetes after the onset of development of HCV.
- Group I are lean subjects according to BMI (BMI<25).

Exclusion criteria:

Patients with any of :

- Concomitant HBV/HIV infection.
- Hepatic focal lesions.
- Liver cirrhosis evidenced clinically/ biochemically/ or by Fib4 equation.
- Thyroid disease.
- Autoimmune disease.
- Malignancy or renal impairment.

All subjects were subjected to:

1. A Full medical history was taken from both groups including the patient's age, sex, history of HTN, family history of diabetes.
2. Complete physical examination (recording systolic and diastolic blood pressure, weight, height and BMI, waist circumference).
3. CBC, liver enzymes, kidney function tests, random blood sugar, HCV antibody, HCV RNA for group I, islet cell antibody, Fib4 for group I.
4. Abdominal ultrasound examination.

Islet cell antibodies:

The ICA test is a qualitative ELISA test for in vitro detection of circulating IgG antibodies against pancreatic islet cell antigens **(Srikanta et al., 1985).**

Principle of the test:

A purified mixture of pancreatic antigens is immobilized onto microwells. During an incubation period, antibodies in the serum sample are allowed to react at room temperature with antigen molecules on the microwells. After washing off excess/unbound serum materials, an enzyme (alkaline phosphatase) labeled goat antibody, specific to human IgG, is added to the antigen-antibody complex. After another thorough washing, a substrate (PNPP) is added and the color generated is measured spectro-photometrically, the intensity of the color is directly proportional to the concentration of ICA in the sample. An ICA-positive control serves as an internal quality control and ensures valid results **(Rossini et al., 1989).**

Fib4 calculation:

The FIB-4 values were calculated automatically using the formula:

Age (years) × AST [U/L] / (platelets [10^9/L] × (ALT [U/L])$^{1/2}$).

The Fib4 represents an easy-to-use test for predicting severe hepatic fibrosis or cirrhosis. Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase **(Vallet-Pichard et al., 2007).**

Ethical consent:

An approval of the study was obtained from Fayoum University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Statistical Analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Simple descriptive analysis in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, standard deviations as measure of dispersion for quantitative parametric data. Quantitative data included in the study was first tested for normality by One-Sample Kolmogorov-Smirnov test in each study group then inferential statistic tests were selected. Chi square test (χ^2) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). Mann-Whitney U Test was a test of significance used for comparison between two groups having quantitative variables without normal distribution. One way ANOVA test in comparing more than two independent groups of quantitative data. Difference among 3 independent means was analyzed using Kruskal-Wallis test (KW) for non-parametric variables. P-value ≤ 0.05 was considered the cut-off value for significance.

3. Results

In this study males represent around 53% in both group I and group II, while females represent around 47 % and the differences were statistically non-significant. The mean age was high among group I compared to group II and difference was statistically significant (p-value 0.003), and family history of diabetes was positive among group II and negative among group I difference was statistically significant (p-value<0.001), group I show high percentage of males than group II, (p-value, 0.04) (Table 1).

The anthropometric measures the mean BMI, Waist circumference was significant higher in group II compared to group I (p-value (<0.001). On the other hand there was no statistical significance difference between groups as regards mean systolic, diastolic blood pressure.

Table (1): Comparisons of demographic characters in different study groups.

Variables	Group I (n=40)	Group II (n=40)	P-value
Age (years) Mean+SD	52.4+10.6	49.2+6.8	0.1
Gender Male Female	26 (65%) 14 (35%)	21 (52.5%) 19 (47.5%)	0.4
Family history Negative Positive	**40 (100%)** 0 (0.0%)	13 (32.5%) 27 (67.5%)	**<0.001**
Prevalence of Hypertension Negative Positive	21 (52.5%) 19 (47.5%)	23 (57.5%) 17 (42.5%)	0.8

The mean of liver enzymes was high among group I compared to group II; (p-value <0.001) and the mean platelet count, in group I was lower than the mean platelet count in group II (p-value 0.02). The mean TLC in group I was lower than the mean TLC in group II but the results were statistically non-significant (p-value 0.2), and also there was no statistical significance difference as regards Hb between group I, group II (p-value 0.06).

The mean RBS was high among group I compared to group II and difference was statistically highly significant (p-value 0.009). Group I show statistically significant high percentage of bright liver (90%) versus (50%) among group II (p-value <0.001).

There was no statistically significant difference between group I, group II as regards the positivity of internal carotid artery (ICA) (p-value 0.9), the prevalence of positive ICA was 16.3% of total study group, the prevalence of patients with positive ICA in group I is 17.5%, the prevalence of patients with positive ICA in group II is 15% (Table 2).

Table (2): Comparisons of anthropometric measures and blood pressure, routine investigations, liver echogenicity and positivity of internal carotid artery (ICA) in different study groups.

Variables	Group I (n=40) Mean± SD	Group II (n=40) Mean± SD	P-value
Anthropometric measures			
BMI (kg/m^2)	22.3 ±1.3	34.6 ±4.5	**<0.001**
WC(cm)	91.9 ±12.8	112.8±7.4	**<0.001**
Blood pressure			
Systolic	137±24.8	135±19.7	0.7
Diastolic	85.3±13.9	83±12.6	0.5
Liver enzymes			
ALT	58.7±36.4	21.7±14.2	**<0.001**
AST	57.1±29.5	26.1±17.2	**<0.001**
Complete blood count			
HB	12.2±0.91	11.9±0.65	0.06
TLC	6.6 ±2.3	7.3 ±2.1	0.2
PLT	204.6±75.1	236.9±45.9	**0.02**
Other investigations			
RBS	218.1±89.6	176.2 ±43.4	**0.009**

Liver echogenicity: N (%) Bright Normal	 36 (90%) 4 (10%)	 20 (50%) 20 (50%)	**<0.001**
Internal carotid artery: N (%) Positive Negative	 7 (17.5%) 33 (82.5%)	 6 (15%) 34 (85%)	0.9

The mean age in antibody positive patients in the among group I was higher than the mean age in antibody negative patients, and the difference was statistically significant difference p-value (0.02), but on the other hand there was no statistically significant difference as regards sex distribution between patients with positive ICA and patients with negative ICA among group I. also there was no statistically significant difference between patients with positive ICA and patients with negative ICA as regards liver echogenicity (p-value 0.6) (Table 3).

There was no statistically significant difference between patients with positive ICA versus patients with negative ICA among group I as regards the anthropometric measures (BMI, and WC) or blood pressure measures (p-value >0.05). Also there was no statistically significant difference in liver enzymes, complete blood picture and level of RBS, PCR, and Fib4 between patients with positive and negative ICA (p-value >0.05) (Table 3).

Among group II patients there was no significant difference between patients with positive and negative ICA (p-value >0.05), as regards age, sex distribution and liver echogenicity findings.

Among group II there was no statistically significant difference between patients with positive ICA versus patients with negative ICA as regards anthropometric measures (BMI, and WC) or blood pressure measures and (p-value >0.05). Also there was no statistically significant difference as regards liver enzymes, complete blood picture and level of RBS, PCR, and Fib4 between patients with positive and negative ICA (p-value >0.05) (Table 4).

Table (3): Comparisons of demographic characters, radiological findings and different study variables in patients with positive ICA versus patients with negative ICA among group I.

Variables	Positive ICA (n=7)	Negative ICA (n=33)	P-value
Age (years) Mean±SD	 61.6±7.6	 51.1±10.9	**0.02**
Gender Male Female	 5 (71.2%) 2 (28.6%)	 18 (54.5%) 15 (45.5%)	0.7
Liver echogenicity Bright Normal	 6 (85.7%) 1 (14.3%)	 30 (90.9%) 3 (9.1%)	0.6
	Mean±SD	**Mean±SD**	
Anthropometric measures BMI (kg/m^2) WC (cm)	 22.3 ±1.4 90.1 ±12.9	 22.3 ±1.3 92.2 ±12.9	 0.9 0.7
Blood pressure Systolic Diastolic	 142.9±21.4 90 ±15.3	 135.8 ±25.6 84.2 ±13.7	 0.5 0.3
Liver enzymes ALT AST	 56.1 ±14.1 50.8 ±9.7	 44.8 ±17.6 43.9 ±16.9	 0.1 0.3
Complete blood count HB TLC PLT	 12.9 ±1.4 7.02 ±2.9 192.3±75.9	 12.4 ±1.03 6.5 ±2.2 207.2±75.9	 0.3 0.6 0.6
Other investigations RBS PCR Fib 4	 249±81.5 2282573.1±1953698.9 1.6±1	 211.5±90.9 839486.6±1008448.5 2.1±2.4	 0.3 0.06 0.6

Table (4): Comparisons of demographic characters, radiological findings and different study variables in patients with positive ICA versus patients with negative ICA among group II.

Variables	Positive ICA (n=6)	Negative ICA (n=34)	p-value
Age (years)			
Mean ±SD	47.7±7.2	49.4±6.8	0.6
Gender			
Male	4 (66.7%)	17 (50%)	0.7
Female	2 (33.3%)	17 (50%)	
Liver echogenicity			
Bright	3 (50%)	17 (50%)	0.9
Normal	3 (50%)	17 (50%)	
	Mean±SD	**Mean±SD**	
Anthropometric measures			
BMI (kg/m^2)	33.7±6.1	34.8 ±4.2	0.6
WC (cm)	110.7±5.7	113.2 ±7.7	0.4
Blood pressure			
Systolic	136.7±19.7	134.7 ±20	0.8
Diastolic	83.33±12.1	82.9 ±12.9	0.9
Liver enzymes			
ALT	22.3±17.8	21.6 ±13.8	0.9
AST	25±20.4	26.3 ±16.9	0.8
Complete blood count			
HB	11.8±0.7	11.9±0.6	0.7
TLC	7.3±2.2	7.3±2.1	0.8
PLT	245±45.1	235.4±46.7	0.9
Other investigations RBS	173.5±30.8	176.6±45.6	0.6

4. Discussion

In the current study, group I included a higher percentage of males compared to group II as males represented 57.5% of group I but only 32.5% of group II.

This result was in agreement with a study done by **Elhawary et al. (2011)** who reported that Males represented 72.5% of the diabetic HCV cases but only 16.7% of diabetic controls.

This results disagree with **Farshadpour et al. (2018)** who stated that there was no difference in gender distribution between the HCV-seropositive and HCV-sero-negative diabetic patients.

This study found that more patients in group II gave a positive family history of diabetes than in group I with statistically significant difference between the 2 groups (P value<0.001). These results were in agreement with **Coppo et al. (2015)** that reported that a higher percentage of HCV-negative patients reported positive family history for T2DM compared with HCV-positive patients (86.3% vs 56.6%, p = 0.003), this coincides with the work of **Ndako et al. (2009)** who indicated that liver injury per se was associated with DM and that a family history of DM was only an adjunctive factor.

Awadallah et al. (2017) reported that there is significant association exists between chronic HCV-4 infection and systemic hypertension especially among diabetic patients as their study revealed a significant higher prevalence of essential HTN among patients with chronic HCV infection.

There are strong evidences to support the notion that HCV predisposes to IR and other metabolic disturbances with their potential consequences such as cardiovascular complications **(Adinolfi et al., 2012).** Through increasing oxidative stress, IR, and glucose intolerance, HCV results in hyperuricemia, arterial hypertension, and atherosclerosis, thus damaging the cardiovascular system **(Kralj et al., 2016).**

This study showed that there is no statistical significance difference between groups as regards mean systolic or diastolic blood pressure.

This study agree with **Greca et al. (2012)** who stated that there was no difference between HCV+ and HCV-negative (HCV-) patients concerning systolic or diastolic blood pressure.

This study disagree with **Mohamed et al. (2016)** who reported that the mean systolic and diastolic blood pressure (SBP and DBP) for diabetic HCV patients were (126.6 mmHg ± 9.7) and (82.6 mmHg ± 7.9) respectively, which were higher than the mean SBP (122.6 ± 8.8) and DBP (80 ± 6.5) in non HCV diabetic patients.

Inclusion of lean patients in group I and lack of metabolic syndrome components can explain our different results regarding hypertension.

The current study showed that the mean platelet count in group I was lower than the mean platelet count in group II (p-value 0.02) and the mean TLC in group I was lower than the mean TLC in group II but the results were statistically non-significant (p-value 0.2).

These results were in agreement with **Greca et al. (2012),** who stated that Platelet and leukocyte counts were lower in HCV+ diabetic patients than patients with HCV negative diabetic patients.

This study found that there is no statistical significance difference as regards Hb level between group I and group II.

El-kafrawy et al. (2011) also did not find any significant difference between hemoglobin of patients in two groups i.e. HCV positive with diabetes and HCV negative with diabetes.

Having hepatitis C virus (HCV) can worsen glycemic control in patients with type 2 diabetes (T2D). In patients who developed a sustained virologic response (SVR), both hemoglobin (Hb) A1c levels and use of insulin decreased as compared with patients who did not achieve SVR **(Hum et al., 2017).**

The current study showed that the mean random blood sugar was high among group I compared to group II and difference was statistically highly significant (p-value 0.009).

These results agree with **Bashir et al. (2013)** who reported that HCV + diabetes patients have shown more elevated levels of HbA1C, fasting blood glucose and random blood glucose than diabetics patients only.

In the present study, there was no statistically significant difference between group I, group II as regards the positivity of ICA (p-value 0.9), the prevalence of patients with positive ICA in group I is 17.5%.

This result was in agreement with **Parchman et al. (2007)** as there was no statistically significant difference could be detected in ICA distribution among HCV positive diabetics and HCV negative non diabetics, but they disagree with our study as their study showed the prevalence of islet cell antibody was 3.75% only in the studied group. hey concluded that an autoimmune mechanism does not seem to be responsible for the development of diabetes in HCV infected patients.

Another study was done by **Piquer et al. (2001)** and they tested ICA, GADA, anti-IA2 in HCV infected diabetic patients and they did not detect any positive cases of GADA, anti-IA2, or ICA.

This result disagree with **Zhang et al. (2006)** who reported that Chronic hepatitis patients with diabetes had much higher positivity rate for islet cell antibody than type 2 diabetic patients with liver dysfunction, but the chronic hepatitis in their study was due to HBV and not HCV.

The current study indicated the mean age in antibody positive patients in group I was higher than the mean age in antibody negative patients, but on the other hand there is no statistically significant difference as regards sex distribution between patients with positive ICA and patients with negative ICA among group I. Also there was no statistically significant difference between patients with positive ICA and patients with negative ICA as regards liver echogenicity (p-value 0.6).

This study also showed no statistically significant difference between patients with positive ICA versus patients with negative ICA among group I as regards the anthropometric measures (BMI and WC) or blood pressure measures (p-value >0.05). Also there is no statistically significant difference in liver enzymes, complete blood picture and level of RBS, PCR, and Fib4 between patients with positive and negative ICA (p-value >0.05).

Up to our knowledge, there were no studies comparing ICA positive HCV diabetic patients versus ICA negative HCV diabetic patients as regard age, sex, liver echogenicity, anthropometric measures, liver enzymes, complete blood picture and level of RBS, PCR, and Fib4.

The prevalence of patients with positive ICA in group II (type 2DM) is 15%. Similar study was done by **Davis et al. (2005)** who found that 11.6% of type 2 DM had antibodies to at least one of three antigens: islet cell cytoplasm, glutamic acid decarboxylase and islet autoantibody 2A (IA-2A).

Another study was done by **Zaharieva et al. (2017)** who reported that the prevalence of positive diabetes-associated autoantibodies among patients diagnosed with T2D is 10.16%, GAD65As were the main positive autoantibody and followed by IA-2A.

In the current study group II patients showed no significant difference between patients with positive and negative ICA (p-value >0.05), as regards age and sex distribution and liver echogenicity findings, anthropometric measures (BMI, and WC) or blood pressure measures, liver enzymes, complete blood picture and level of RBS, PCR, and Fib4 (p-value >0.05).

This results disagree with **Davis et al. (2005)** who reported that When compared with Ab−ve patients, those who were Ab+ve type II diabetic patients were younger ($p<0.0001$) and tended to be female, rather than male, also Ab+ve type 2 diabetic patients were leaner ($p<0.0001$),and they had lower systolic ($p<0.0001$) and diastolic ($p<0.0001$) blood pressure and this may be due to that not all Ab+ve type 2 diabetic patients were ICA antibody positive but they represent 1.5% of the group.

The prevalence of positive ICA was 16.3% of total study group. This result agree with **Brooks-Worrell et al. (2014)** who stated that by Using islet autoantibodies as a biomarker for islet autoimmunity for type 2 DM, the prevalence of islet autoimmunity has been estimated to be between 5-30%.

Conclusion

Islet cell antibodies do not appear to play a significant role in the pathophysiology of diabetes in HCV infected patients.

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6/22/2021