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Relationship between HCV infection and Insulin resistance in non-obese non-diabetic patients

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Abstract

Background: Hepatitis C is a major cause of liver-related morbidity and mortality and represents a major public health problem in Egypt and worldwide. There is growing evidence as regard to the association between hepatitis C virus (HCV) infection and type 2 diabetes mellitus. However, the mutual link and related virological implication have not been fully clarified. Insulin resistance (IR) plays a primary role in the development of type 2 DM. This is supported by the results of prospective longitudinal studies showing that IR is the best predictor of the development of type 2 DM, preceding its onset by 10-20 years.

Aim: To assess the correlation between HCV morbidity and Insulin resistance (IR) detected by HOMA test in none diabetic none obese HCV patients

Materials & Method: The study participants were subcategorized into two groups,Group (I): included 867 healthy subjects (negative HCV RNA) as a control group. Group (II): included 277 patients with chronic HCV as a study group. The 2 groups were subjected to thorough history taking, full clinical examination, Anthropometric study,ultrasonographic examination and laboratory investigations including liver functions, viral markers, and qualitative PCR for HCV RNA ,lipid profile, glucose profile and HOMA test .

Results: This study revealed higher insulin resistance in the HCV study group than the control group.

Key words: HCV-Insulin resistance,HOMA test

Introduction:

The incidence of noncommunicable diseases (NCDs) such as cardiovascular disease (CVD), diabetes, cancer, renal, genetic and respiratory diseases is rising significantly in the Eastern Mediterranean Region .In Egypt noncommunicable diseases account for about 42% of the total deaths while CVD accounts for about 22% of deaths ***(WHO, 2004).*** Hepatitis C is a major cause of liver-related morbidity and mortality and represents a major public health problem in Egypt and worldwide ***(Alberti and Benvegnu, 2003)*** and there is a large underlying reservoir of HCV-caused liver disease ***(Strickland et al., 2002).*** The countries of the Eastern Mediterranean Region are, therefore, suffering from a double burden of both communicable and noncommunicable diseases ***(WHO, 2004).*** The link between communicable and noncommunicable diseases could exist. In some studies, chronic infections have been found to be associated with atherosclerosis ***(Leinonen and Saikku, 2002).***There is growing evidence as regard to the association between hepatitis C virus

(HCV) infection and type 2 diabetes mellitus. However, the mutual link and related virological implication have not been fully clarified ***(Jee-Fu et al,2007).***Insulin resistance (IR) plays a primary role in the development of type 2 DM. This is supported by the results of prospective longitudinal studies showing that IR is the best predictor of the development of type 2 DM, preceding its onset by 10-20 years. (IR) is widely regarded as an important component of type 2 DM. Some authors have used the term 'insulin sensitivity', which is the reciprocal of insulin resistance, because the term 'normal insulin sensitivity' is more meaningful than 'normal insulin resistance' ***(Haffner, 1997).***

IR describes a state where there is reduced biological effect for any given concentration of insulin ***(Hunter and Garvey, 1998).***Insulin resistance is an independent risk factor for cardiovascular disease and Type 2 DM. Hypertension, dyslipidaemia and obesity are often found in association with IR. However the presence of these conditions cannot be used as evidence of the coexistence of IR ***(Opara and Levine, 1997).***Although ***Himsworth*** and others had described insulin-resistant diabetic patients in the late 1930s based on dosages required, **Yalow *and Berson*** (1968) (who described the insulin immunoassay) showed that insulin concentrations were higher in those with Type 2 DM. This was the first description of IR based on plasma measurements of the hormone.

IR can be ***physiological***, as occurs in pregnancy and in puberty, or ***pathological***. It may occur as a primary phenomenon, be secondary to other disorders, or may arise as a result of specific defects such as insulin receptor mutations. The commonest described state of IR is the metabolic syndrome (Syndrome X, Reaven's syndrome, Type 2 DM, the IR syndrome) which is characterized by the combination of IR, hyperglycaemia, hypertension, dyslipidaemia (low HDL, small dense LDL, high triglycerides), hyperuricaemia and obesity ***(Haffner and Miettinen ,1997).***

Methods for assessing insulin resistance:

I-Insulin dose

II-Insulin concentration in plasma

III-Quantitative estimates of insulin resistance

1-MODELS

a) Homeostasis Assessment Model (HOMA)
b) Continuous Infusion of Glucose with Model Assessment (CIGMA)
c) Quantitative insulin-sensitivity check index (QUICKI)
d) McCauley index
e) HOMA-AD
f) Fasting insulin glucose ratio (FIG)
g) Frequently sampled intravenous glucose tolerance test (FSIGTT)

2-Clamps

I) Euglycaemic clamp
II) Hyperglycemic clamp

3-Insulin infusion sensitivity tests

I) Insulin sensitivity test (IST)
II) Short insulin tolerance test (ITT)

4-Oral glucose tolerance test

The Homeostasis Assessment Model (HOMA)is a mathematical model, which allows values for insulin sensitivity and β-cell function (expressed as a percentage of normal) to be obtained if simultaneous fasting plasma glucose and fasting insulin are known ***(Matthews et al., 1985).*** Since insulin secretion is pulsatile, the optimal sample should be the mean of three results at 5-min intervals (0, 5, and 10-min samples). However, many researchers have used single basal samples for epidemiological studies. HOMA has proved to be a good method for assessing insulin resistance in groups of patients over long periods of time because the sampling is simple, and the result is available without complex computing as soon as fasting glucose and insulin values are available ***(Emoto et al., 1999).*** Estimates of insulin resistance from HOMA correlate well with estimates from the euglycaemic clamp ***(Bonora et al., 2000)***. In contrast to other methods, HOMA gives an estimate of basal insulin resistance, whereas all other tests provide estimates of stimulated insulin resistance.

HOMA produces a formula for insulin

resistance (R_{HOMA}) calculated as:

$$\frac{\text{Fasting glucose (mmol/l) X Fasting insulin (µIU/ml)}}{22.5}$$

In addition, HOMA was used to calculate beta-cell function as percentage of normal (%) using the formula:

$$\frac{\text{20 X Fasting insulin (µIU/ml)}}{\text{Fasting glucose (mmol/l) - 3.5}}$$

The cutoff value for insulin resistance in HOMA is a matter of debate, ***(Nakai et al., 2002) (Taniguchi et al., 2000)*** defined the value > 2.5 as an insulin-resistant state based on the HOMA-IR value. While ***(Sihoon Lee et al., 2006)***, in their study, found that the cutoff point for defining insulin resistance is a HOMA-IR=3.04. ***Bonora et al., 1998*** defined 2.77 as cutoff value for insulin resistance in HOMA score.

Relationship between HCV, DM and insulin resistance in various stages of disease:

1- HCV Chronic hepatitis and insulin resistance:

An increased prevalence of diabetes among HCV-infected patients with chronic hepatitis compared with either subjects with other chronic liver disease or the general population has been consistently reported***(Özylilkan and Arslan, 1996) (Mangia et al., 1998).***The prevalence not only of diabetes but also the impaired fasting glucose (IFG) in a large cohort of HCV-infected patients, was also found ***(Mason et al., 1999).***

2-HCV liver cirrhosis and insulin resistance:

When HCV-infected patients with cirrhosis are evaluated, the prevalence of type 2 diabetes is higher than reported in patients with chronic hepatitis, and it ranges from 19.6 to 50% ***(Garrido et al.,2001) (Parolin et al.,2004).(Thuluvath and John, 2003)*** found no significant difference between cirrhotic patients with or without HCV infection. Therefore, it seems that the presence of advanced liver disease is an even stronger diabetogenic factor than HCV infection itself. In other words, diabetes associated with HCV infection is less of a determinate than the effect of hepatic cirrhosis on glucose metabolism ***(Zein et al., 2000).***Also, ***(Lecube et al., 2004)*** did not observe differences between cirrhotic patients with or without HCV infection. These findings suggest that the genuine connection between HCV infection and diabetes is initiated at the early stages of hepatic disease. They detected a five fold-higher prevalence of diabetes than that found among anti–HCV-negative patients (24 vs. 5%).

3-HCV infection as a risk factor for post-transplant diabetes:

Post-transplantation diabetes mellitus (PTDM) is a common medical condition arising during the follow-up of renal and liver transplant recipients, which has increased in incidence over the last decade ***(Cosio et al., 2001).***A number of risk factors related to the recipient, the immunosuppressive agents used to prevent and treat rejection, and donor source have been described as independent risk factors for the development of PTDM***(Kasiske et al., 2003).***The prevalence of PTDM in HCV-infected liver transplantation recipients ranges from 40 to 64%, significantly higher than the prevalence reported in transplanted patients for other causes of liver failure ***(Bigam et al., 2000).***In addition, HCV has been found to be an independent risk factor for diabetes development after transplantation. Furthermore, ***(Baid et al., 2001)*** reported a close temporal relationship between the recurrence of HCV hepatitis in the allograft and the onset of PTDM in approximately half of the HCV-positive patients with PTDM.HCV infection may reach an incidence of 50% in patients with end-stage renal disease, and it has also been identified as an independent risk factor for predicting the development of PTDM after renal transplantation ***(Yildiz et al., 2002).***

All these data reinforce the hypothesis that HCV is the cause rather than the consequence of diabetes. In addition, the link between HCV and diabetes may contribute substantially to the detrimental role of HCV on patient and graft survival after liver transplantation and/or renal transplantation ***(Abbott et al., 2004).***

Patients and methods:

It is a prospective study for 1144 participants recruited through a cohort from a village in Monoufia governorate in Delta region of Egypt. The study protocol was approved by the Egyptian Ministry of Health and Population Institutional Review Board and a

local ethics committee set up for hepatitis studies in Egypt.The study participants were subcategorized into two groups:
Group (I): included 867 healthy subjects (negative HCV RNA) as a control group.
Group (II): included 277 patients with chronic HCV as a study group.
Inclusion criteria were adult patients >18 years old,positive serology for HCV and HCV viremia,none diabetic (negative history and fasting blood sugar level<126 mg/dl) and none obese (BMI < 30).
Exclusion criteria were negative HCV viremia,positive HBsAg,diabetic patients (known diabetic or FBS >126 mg/dl) and obese patients (BMI > 30).
All participating subjects, after a written consent, were subjected to the following **I-** careful history taking, Including age, present and past occupation and residence ,history of drug or alcohol intake ,history of schistosomiasis and previous parenteral treatment for it , history of blood transfusion ,dental procedure and operations. Any associated disease as diabetes mellitus or hypertension and any present complaint **II-** Thorough clinical examination.**III.** Anthropometric study was done for all studied patients focusing on evaluation of body mass index (BMI) which is equal to weight/height 2 (in kg/m2); with BMI ranging between 19 to 25 kg/m2 refer to normal average. BMI of 30 or more is most commonly used as threshold for obesity while BMI between 25 and 30 are suggesting overweight ***(CDC, 2009).*****IV.** Laboratory assays including:
a) Glucose profile(Fasting glucose- Specific insulin assay- C-peptide)
b) Liver function tests(AST,ALT,Bilirubin,Albumin,ALP,INR)
c) Viral markers(HBs Ag, HBc Ab and HCV Ab)
d)Qualitative HCV RNA by PCR.
e) Homeostasis model assessment (HOMA) score estimation

Laboratory assays:
Blood sampling, about 10 ml venous blood were obtained from each individual, 2 ml were collected in a tube containing dipotassium EDETA as an anticoagulant for qualitative detection of HCV RNA ,another 1.8 ml were collected in a tube containing 0.2 ml sodium citrate for PT detection. The remaining 6 ml were collected in a plain tube, allowed to clot and centrifuged to get serum. Blood glucose and liver function tests were done immediately after centrifugation, the remaining serum was stored at -20 oC as aliquots for demonstration of insulin level, C peptide, and viral markers.

The laboratory evaluations include:

A-Glucose profile: fasting glucose level was measured by enzymatic colorimetric method using kit provided from Human, Germany. Insulin level and C-peptide were demonstrated in serum by using semi-automated ELISA system (TC,96, USA), kit provided from DRG International,USA .The absorbance values were read using ELISA reader at wave length 450+10 nm for both insulin and C-peptide***(Chieregatti,1999).***
The concentrations were calculated using computer software capable of generating a four parameters algorithm.
*Calculation of insulin resistance according to HOMA score (homeostasis model assessment), ***(Matthews et al., 1985).***using the following:
HOMA insulin resistance score=

$$\frac{\text{Fasting glucose (mmol/l x insulin (}U\text{u/ml)}}{22.5}$$

B-Liver function tests and lipid profile were measured by semi automated chemical analyzer (Chem 7 plus,Germany), using kit provided from ELI Tech, France,for AST,ALT and ALP and from Human, Germany for albumin, bilirubin, PT and serum lipid.

C-Viral laboratory assessment:
1.Serological tests for HBsAg, HBcAb and HCVAb by ELISA technique***(Chieregatti,1999)***, using kit provided from EIA gen, Adaltis, Italy. The color intensity was measured at 450 nm with reference filter 620- 630 nm. The concentrations have been calculated automatically using 4 parameter logistics computer software.
2. Qualitative detection of HCV RNA by the method of Reverse Transcriptase PCR, this falls into four main steps:
*HCV RNA extraction using the QIAmp Viral RNA kit, Germany, then this is followed by c-DNA synthesis within 3 hours or stored at -80 OC for up to one month with no more than one freeze-thraw.
*Reverse transcription of extracted HCV RNA into complementary DNA(c- DNA) and first

round PCR amplification using primers for HCV, the sequences of the primers were as follows:
P1 5'AACTACTGTCTTCACGCAGAA3'
P2 5'GGTGCACGGTCTACGACCTC3'.
The amplification procedure was performed by thermal cycler apparatus (PTC-200, USA) programmed as follows; 42°C for 30 min; 95ºC for 5 min followed by 30 cycles (94ºC for 1 min, 55°C for 1 min and 72°C for 1 minute) and finally 72°C for 5 min.
*Second round PCR amplification was performed in a thermocycler programmed as follows; 95ºC for 5 min followed by 30 cycles (94ºC for 1 min, 55°C for 1 min and 72°C for 1 minute) and finally 72°C for 5 min, using primers with sequences as follows:
P3 5'GTGCAGCCTCCAGGACCC3'
P4 5'ACTCGGCTAGCAGTCTCGCG3'.
*Detection of the amplified fragments by loading the amplified products on 2.5% agarose gel and visualized using UV transilluminator. Band sizes were compared to a 50-bp DNA ladder. A fragment of 171bp length was identified as a positive sample.

Statistical analysis:

We used following software in our research statistics SPSS version 16 and Microsoft excel with analyze-it add in.Description of qualitative variables by frequency and percentage.description of quantitative variables in the form of mean and standard deviation (mean ± SD).Chi-square (x2) test was used for comparison of qualitative variables with each other.Comparison between quantitative variables was carried by using student t-test of two independent samples.One way ANOVA test (analysis of variance) was used instead of t-test for comparison of more than two quantitative groups.Kruskal wallis ANOVA test used for categorical data.Significance level (p) was expressed as following:P value > 0.05 is insignificant,P value < 0.05 is significant and P value < 0.001 is highly significant.Correlation studies were done using person test for quantitative data and spearman test for categorical data.

Results

	Group I		Group II		
	Mean	**SD**	**Mean**	**SD**	**P Value**
Weight(Kg)	**65.96**	**10.40**	**66.91**	**10.08**	**> 0.05**
Height(cm)	**162.19**	**8.88**	**164.35**	**8.75**	**< 0.05(S)**
BMI	**25.02**	**2.97**	**24.76**	**2.85**	**> 0.05**
waist(cm)	**79.76**	**9.91**	**80.52**	**9.87**	**> 0.05**

Table (1): Demographic features of the studied groups.

Age distribution of the studied patients was shown in table (1), there is significant difference between the mean ages in the 2 groups being higher in the study group than the control group, Group (I) included 387 males (45%) and 480 females (55%).Group (II) included 175 males (63%) and 102 females (37%).

Table (2) physical parameters of the studied groups.

	Group I (non infected N= 867)		**Group II (chronic HCV N=277)**		**P value**
Age					
mean±SD	**41.42**	**14.30**	**46.75**	**11.57**	**<0.05(S)**
Sex					
Males	**387.00**	**45%**	**175.00**	**63%**	
Females	**480.00**	**55%**	**102.00**	**37%**	

Being important influencing factors, Table (2) shows no significant difference was found between both groups as regarding weight, waist circumference and BMI.

	Group I		Group II		
	Mean	**SD**	**Mean**	**SD**	**P Value**
AST (10-42 Iu/L)	**23.00**	**12.03**	**42.45**	**29.75**	**< 0.05(S)**
ALT (10-40 Iu/L)	**20.24**	**11.24**	**43.77**	**37.79**	**< 0.05(S)**
ALB(g/dl)-(3.5-5.0)	**3.95**	**0.41**	**3.85**	**0.48**	**< 0.05(S)**
TBIL(mg/dl)-(0.1-1.0)	**0.65**	**0.36**	**0.82**	**0.42**	**< 0.05(S)**
DBIL(mg/dl)-(0-0.2)	**0.13**	**0.13**	**0.20**	**0.14**	**< 0.05(S)**
IND BILI(mg/dl)-(0-0.8)	**0.53**	**0.29**	**0.63**	**0.32**	**< 0.05(S)**

Table (3): Liver functions of the studied groups.

Table (3) describes the liver functions of the studied groups, AST, ALT and total,direct and indirect bilirubin are significantly higher in the study group while albumin is significantly higher in the control group.

	Group I		Group II		
	Mean	**SD**	**Mean**	**SD**	**P Value**
F.B.S(mg/dl)	**80.63**	**9.36**	**81.62**	**9.26**	**> 0.05**
Insulin (µU/ml)	**3.87**	**2.70**	**4.91**	**3.82**	**< 0.05(S)**
HOMA	**0.83**	**0.60**	**1.09**	**0.93**	**< 0.05(S)**
C-Peptide(0.6-13.06 ng/ml)	**1.29**	**1.28**	**1.18**	**1.20**	**> 0.05**

Table (4): Glucose profile of the studied groups.

As shown in table (4) Comparing HOMA-Score in both groups, the test was significantly higher in the study group than the control group, also serum insulin level being one of the HOMA equation components is significantly higher in the study group than in control group, meanwhile, the fasting blood sugar and c-peptide show no significant difference between both groups.

		Age in Years
HOMA	Correlation Coefficient	-.049
	Sig. (2-tailed)	.479
		AST
	Correlation Coefficient	.157*
	Sig. (2-tailed)	.023
		ALT
	Correlation Coefficient	.212**
	Sig. (2-tailed)	.002
		ALB
	Correlation Coefficient	-.117
	Sig. (2-tailed)	.092
		T.BIL
	Correlation Coefficient	.117
	Sig. (2-tailed)	.093
		D.BIL
	Correlation Coefficient	.045
	Sig. (2-tailed)	.516
		BMI
	Correlation Coefficient	.359**
	Sig. (2-tailed)	.000

Table (5): Nonparametric correlations (spearman correlation) between HOMA and other parameters

Table(5) shows nonparametric correlations (spearman correlation) between HOMA index and age,AST,ALT, albumin, T.bilirubin, D.bilirubin and BMI , we observe high significant correlation between HOMA index and serum ALT level & BMI ,and significant correlation between HOMA Index and serum AST.These correlations were emphasized through the scattered plot curve (Fig.1) between HOMA versus BMI .

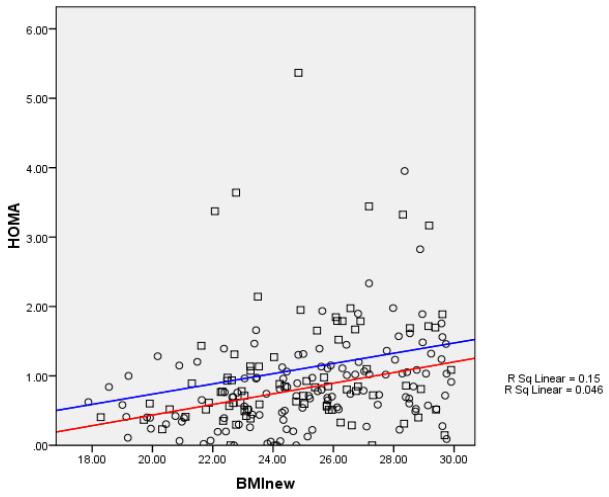

Fig (1): Correlation between HOMA and BMI.

Discussion

Chronic hepatitis C is recognized as a global health problem, with 170 to 200 million people estimated to be infected worldwide. In the United States, chronic HCV is the most common cause of end-stage liver disease, hepatocellular cancer, and the most frequent indication for liver transplantation ***(Alter et al., 1999).***In Egypt the situation is quite worse. Egypt contains the highest prevalence of hepatitis C in the world. The national prevalence rate of HCV antibody positivity has been estimated to be between 10-13% ***(Mohamed MK, 2004).*** Type 2 diabetes (DM), obesity and hypertension (HTN) are associated with overall and liver related mortality in (HCV) infected patients. The top three predictors of liver related mortality were having higher body mass index (BMI), presence of insulin resistance (IR) and elevated serum cholesterol. Overall mortality in HCV patients was most linked to metabolic syndrome, higher BMI and hypertension ***(Rafiq, et al., 2009).***

Our study was conducted on 277 patients with HCV and 867 healthy controls .We studied possible relationships between HCV morbidity and Insulin resistance (IR) detected by HOMA test in none diabetic and none obese patients.

Insulin resistance (IR) has been reported in HCV-infected patients early in the course of HCV infection before the onset of cirrhosis ***(Caronia et al., 1999) (Mason et al., 1999) (Eguchi et al., 2009).This agrees with the results of the current study as we found significant difference in HOMA score estimation between patients with HCV and controls with patients group having higher HOMA score (1.09203± 0.925) than control (0.82783± 0.598) with (p<0.05) which is significant.We also found higher fasting insulin level in HCV patients than control with patients group having higher fasting insulin level (4.9098± 3.8195) than control (3.8708± 2.6964) with (p<0. 05) which is significant. But no significant difference between patients (81.6177 ± 9.2598) and control (80.6306± 9.3639) as regard fasting glucose with (P>0.05) which is not significant.***

Many studies proved that non diabetic HCV-infected patients have higher insulin resistance than patients with other chronic liver diseases ***(Montasser et al., 2005) (Albert et al., 2006).***Recently, it was demonstrated that in non diabetic HCV patients, the clearance of HCV after antiviral therapy induces an improvement in insulin resistance ***(Romero-Gómez et al., 2003) (Kawaguchi et al., 2007).***An improved glucose tolerance has been recognized following liver transplantation in HCV-positive diabetic patients, even without complete regression of IR ***(Tietge et al., 2004).***These previous observations highlight the specific role of HCV in the evolution of impaired insulin action and impaired glucose tolerance, independent from the development of cirrhosis ***(Hui et al., 2003).***Potential mechanisms for HCV induced IR was searched upon in many studies and showed decreased expressions of both IRS-1 and IRS-2 in HCV core transfected human hepatoma cells and in the livers of HCV core transgenic mice and HCV-infected patients ***(Kawaguchi et al., 2004).***Hepatic STAT-3 signaling recently has been shown to play a pivotal role in normal glucose homeostasis and insulin sensitivity and it was also observed that over expression of SOCS-1 and SOCS-3 proteins in obese animal livers enhanced SREBP-1c promoter activity by attenuating signal transducer and activator of transcription 3 (STAT-3)–mediated inhibition of this region. This process produced systemic IR and hepatic steatosis. These observations are relevant in the context of HCV infection, which has been recognized to influence the activity of STAT-3 ***(Ueki et al., 2004).***Collectively, these data suggest that HCV per se is central to the development of IR ***(Ruan et al., 2003).***

Summary

The study assessed HOMA-Score in the studied groups and shows that the test was significantly higher in the study group than the control group; denoting higher insulin resistance in the HCV study group than the control group.

Conclusion

- Chronic HCV is associated with significant insulin resistance.
- Insulin resistance is correlated significantly with higher liver enzymes.

Recommendations

- Evaluation of insulin resistance on a large number of HCV patients in different stages of the disease (chronic, compensated cirrhosis and decompensated cirrhosis) is recommended.
- Study of the correlation between the HCV viral load and the degree of insulin resistance and its status after receiving pegylated interferon and ribavirin as a treatment for HCV.

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العلاقة بين الأصابة بفيروس الإلتهاب الكبدي المزمن "سي" وحدوث مقاومة لتأثير الأنسولين في المرضى الغير مصابين بالسمنة ومرض السكر

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يعتبر فيروس سي الكبدي سببا أساسياً لأمراض الكبد ويمثل مشكلة صحية قومية في مصر .تهدف هذه الدراسة الي تقييم العلاقة بين الأصابة بفيروس الألتهاب الكبدي "سي" وحدوث مقاومة لتأثير الأنسولين فى المرضى الغير مصابين بداء السكري أو السمنة .

اشتملت الدراسة على 1144 شخص تم تقسيمهم كالآتي : 867 شخص سليم (المجموعه الضابطه) غير مصاب بفيروس سي و 277 مريض مصاب بفيروس الألتهاب الكبدي سي.

وقد أظهرت الدراسة وجود مقاومة لتأثير الأنسولين في المجموعة المصابة عن الضابطه بشكل واضح من خلال اسنخدام معامل "هوما " الخاص بقياس مقاومة تأثير الأنسولين بالجسم ، كما أظهرت الدراسة وجود علاقة طردية ذات دلالة بين حدوث مقاومة للأنسولين وبين ارتفاع انزيمات الكبد والدهون الثلاثية