Serum Iron Parameters as Predictors of Insulin Resistance in Non-Diabetic HCV +ve Patients on Chronic Hemodialysis

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Abstract: Background: Hepatitis C virus (HCV) infection is a common problem affecting more than 3% of the world population**.** The problem is more pronounced in hemodialysis centers**.** Insulin resistance is frequently seen in patients with HCV infection. Numerous studies indicated a link of insulin resistance to iron overload. In our study, we aimed to evaluate serum iron parameters as predictors of insulin resistance in non-diabetic HCV+ve patients on hemodialysis. **Subjects and methods:** 60 non-diabetic patients on chronic hemodialysis in Ain Shams university hospital were chosen and divided into 2 groups, **Group 1** consisted of 30 HCV +ve cases and **Group 2**: consisted of 30 HCV -ve cases. All cases were subjected to full history taking and clinical examination with determination of age, sex, BMI and duration of hemodialysis. Serum liver enzymes AST and ALT, FBS, serum fasting insulin were measured with calculation of insulin resistance using the standard homeostatic model assessment (HOMA). Typically, a HOMA-IR>2 is used to identify significant insulin resistance**.** Serum iron parameters including serum iron, serum ferritin, TIBC, TSAT and hemoglobin content were measured for all cases. **Results:** Prevalence of IR in HCV +ve cases on chronic hemodialysis was 86.67% and 33.33% in HCV-ve cases. FBS showed insignificant difference between group 1 and group 2 *(p>0.05).* Meanwhile, insulin and HOMA-IR showed significant increase in group 1 in comparison to group 2 *(p<0.001).* Both liver enzymes (AST and ALT) were significantly higher in group 1 than in group 2 *(p<0.001* for ALT and *=0.001* for AST). S. iron *(p<0.01),* ferritin *(p<0.05),* TSAT *(p<0.05)* and hemoglobin *(p=0.001)* were higher in group 1 than in group 2. **In group 1**, HOMA-IR had a highly significant correlation to both AST *(p<0.01)* and ALT *(p<0.001).* HOMA-IR, also, significantly correlated to serum iron *(p<0.01)* and TSAT *(p<0.01)* but not to serum ferritin, TIBC or hemoglobin *(all p values>0.05).* Also, in group 1 there was a significant correlation between serum iron and both ALT *(p<0.01)* and AST *(p<0.01).* TSAT had a significant correlation only with ALT *(p<0.05)* but not with AST *(p>0.05).* **Conclusion:** it was observed that using HOMA-IR at a cutoff point of > 2, the prevalence of IR in HCV +ve cases on chronic hemodialysis was 86.67% and was 33.33% in HCV-ve cases. Severity of insulin resistance is proportional to the activity of HCV marked by AST and ALT. Serum iron and TSAT are better predictors of insulin resistance than serum ferritin. There is a close relationship between serum iron and (ALT and AST) that might be a complex associate of insulin resistance in HCV +ve cases on chronic hemodialysis.

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1. Introduction

Hepatitis C virus (HCV) infection is a common problem affecting more than 3% of the world population ***(1).*** The problem is more pronounced in hemodialysis (HD) centers where the rate of HCV infection ranges from 1.9% to 84.6%varying from one country to another ***(2).***

Insulin resistance is frequently seen in patients with HCV infection ***(3).*** Hepatic inflammation, active inflammatory cytokines, and HCV-induced impairment of insulin and lipid signaling molecules are important factors underlying the development of insulin resistance ***(4).*** Therefore, the prevalence of insulin resistance is higher in patients with HCV infection compared to that in the general population ***(5).*** Indeed, insulin resistance plays a crucial role in the development of various complications associated with HCV infection like hepatic steatosis, resistance to anti-viral treatment, hepatic fibrosis, esophageal varices, hepatocellular carcinoma and extrahepatic manifestations mainly type 2 diabetes mellitus, cardiovascular diseases and infections***(6).***

Insulin resistance and its associated metabolic abnormalities are known complications of advanced chronic kidney disease (CKD). Previous studies showed that a post binding defect in insulin action, probably resulted from retained uremic toxins, was the primary cause of glucose intolerance in non-diabetic patients with ESRD. Vitamin D deficiency, metabolic acidosis, and inflammation are other potential contributors to the development of insulin resistance in ESRD patients ***(7).***

Numerous studies indicated a link of insulin resistance to hepatic iron overload. Increased serum

ferritin is often associated with insulin resistance ***(8).*** It is increasingly recognized that iron influences glucose metabolism, even in the absence of significant iron overload. In the general population, body iron stores are positively associated with the development of glucose intolerance ***(9).***

In our study, we aimed to evaluate serum iron parameters as predictors of insulin resistance in non-diabetic HCV+ve patients on hemodialysis.

2. Subjects and methods

Our cross sectional observational study was conducted on 60 non-diabetic patients who were on chronic hemodialysis replacement therapy in the dialysis unit of Ain Shams university hospital. Patients were chosen and divided into 2 groups:

Group 1: consisted of 30 HCV seropositive cases.

Group 2: consisted of 30 HCV seronegative cases.

All cases were subjected to full history taking and clinical examination with determination of age, sex, body mass index (BMI) and duration of hemodialysis (in months). Serum liver enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were measured too.

Fasting blood glucose (FBS) and serum fasting insulin were measured. From previous data we could calculate insulin resistance (IR) using the standard homeostatic model assessment (HOMA) equation (HOMA-IR= FBS (mg/dl) X fasting insulin (mU/L)/405).Typically, a HOMA-IR>2 is used to identify significant insulin resistance ***(10).***

Serum iron parameters including serum iron, serum ferritin, total iron binding capacity (TIBC), transferrin saturation (TSAT) and hemoglobin content were measured for all cases.

Known cases of diabetes mellitus, BMI out of normal range (>30 and <18), patients received or on interferon therapy, and patients with severe illness were excluded from the study. Also, cases of schistosomiasis, hepatitis B or HIV infection, acute or chronic infection were excluded.

Statistical analysis:

It was done using a statistical program MINITAB 14 on a personal IBM compatible laptop.

Quantitative data were expressed as mean ± standard deviation. Comparison of quantitative parametric data was done using the paired t test. Qualitative data were compared using chi square test. Linear correlation coefficient was used to detect correlation between two quantitative variables.

3. Results

In our cross sectional observational study, 60 non-diabetic patients on chronic hemodialysis in the dialysis unit of Ain Shams university hospital were chosen and divided into 2 groups, **group 1** consisted of 30 HCV seropositive cases and **group 2** consisted of 30 HCV seronegative cases.

As we can see from **table1,** there was no significant difference between group 1 and group 2 as regards age, sex or BMI rendering both groups liable for comparison *(all p values >0.05).*

Duration of hemodialysis was significantly longer in HCV+ve than HCV-ve patients *(p<0.001).*

FBS showed insignificant difference between group 1 and group 2*(p>0.05).*Meanwhile, insulin and HOMA-IR showed highly significant increase in group 1 in comparison to group 2 *(p<0.001).*

Both liver enzymes (AST and ALT) were significantly higher in group 1 than in group 2 *(p<0.001*for ALT and *=0.001* for AST*).*

As regards iron parameters, iron *(p<0.01),* ferritin *(p<0.05),* TSAT *(p<0.05)* and hemoglobin *(p=0.001)* were higher in group 1 than in group 2 while TIBC showed insignificant difference between both groups *(p>0.05).*

Table 1: Comparison between Group1 and Group 2

	Group 1 HCV +ve N=30	Group 2 HCV –ve N=30	t	P
Age(years)	43.033±11.044	43.167±13.293	0.05	0.960
Sex	21♂9♀	23♂ 7♀	X^2 0.341	0.559
BMI(kg/m²)	25.203±3.118	25.570±2.082	0.67	0.505
Duration of HD(months)	109.667±55.770	37.233±32.075	5.8	0.000
FBS(mg/dl)	82.433±9.329	78.6±9.216	1.81	0.080
Fasting Insulin(mU/l)	14.633±3.548	8.9±2.454	7.75	0.000
HOMA-IR	2.979±0.907	1.774±0.732	6.22	0.000
Incidence of IR	26(86.666%)	10(33.333%)	X^2 4.571	0.033
AST(U/l)	49±29.544	28.533±12.992	3.91	0.001
ALT(U/l)	54.233±34.846	27.933±11.7911	4.22	0.000
IRON(µmol/l)	83.983±52.346	52.367±26.738	2.91	0.007
FERRITIN(µg/l)	659.850±652.129	378.4±286.616	2.06	0.049
TIBC(µmol/l)	301.833±83.481	277.531±78.004	0.98	0.333
TSAT(%)	31.528±21.866	20.143±12.211	2.45	0.020
Hemoglobin(g/dl)	11.223±2.262	9.05±2.021	3.64	0.001

Table 2: HOMA-IR correlations in Group1 and in Group 2

Groups / Correlation of HOMA to	Group 1 N=30		Group 2 N=30	
	r	P	r	P
Age(years)	0.151	0.426	0.215	0.254
BMI(kg/m²)	0.22	0.907	0.173	0.361
Duration of HD(months)	0.171	0.365	0.235	0.212
FBS(mg/dl)	0.567	0.001	0.756	0.000
Fasting Insulin(mU/l)	0.912	0.000	0.958	0.000
AST(U/l)	0.470	0.009	0.379	0.039
ALT(U/l)	0.639	0.000	0.364	0.038
IRON(µmol/l)	0.470	0.009	0.263	0.161
FERRITIN(µg/l)	0.274	0.142	0.189	0.316
TIBC(µmol/l)	0.228	0.226	0.398	0.39
TSAT(%)	0.524	0.003	0.334	0.72
Hemoglobin(g/dl)	0.004	0.983	0.252	0.179

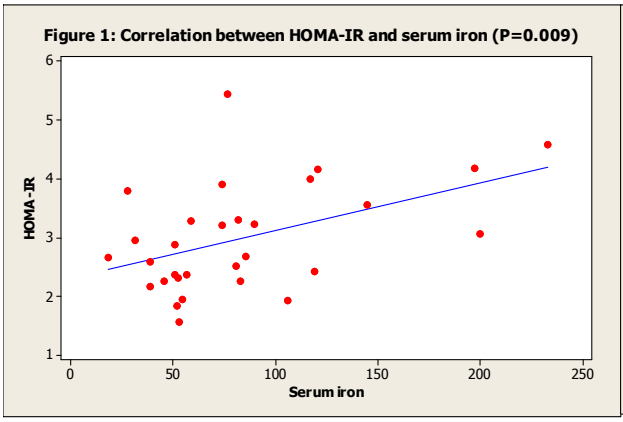
Table 2 shows the correlations of HOMA-IR to different parameters of the study in group 1 then in group 2. **In group 1 (HCV+ve patients)**, HOMA-IR had a highly significant correlation to both AST *(p<0.01)* and LT *(p<0.001)*. HOMA-IR, also, significantly correlated to serum iron *(p<0.01)* and TSAT *(p<0.01)* but there was insignificant correlation between HOMA-IR and serum ferritin, TIBC or hemoglobin *(all p values>0.05)*.

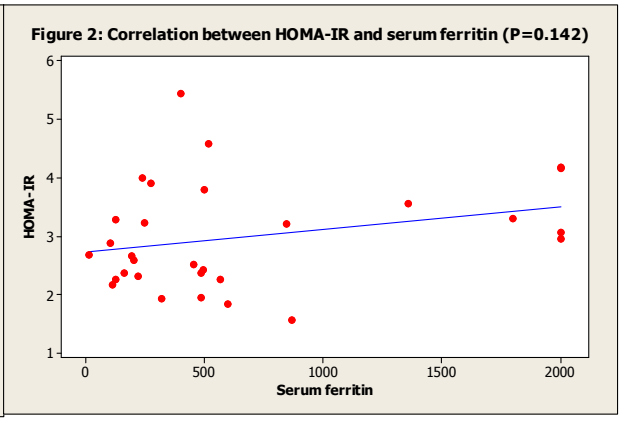
In group 2(HCV-ve patients), there was a significant correlation between HOMA-IR and both AST and ALT *(p <0.05* for both).There was insignificant correlation between HOMA-IR and serum iron, serum ferritin, TIBC or hemoglobin.

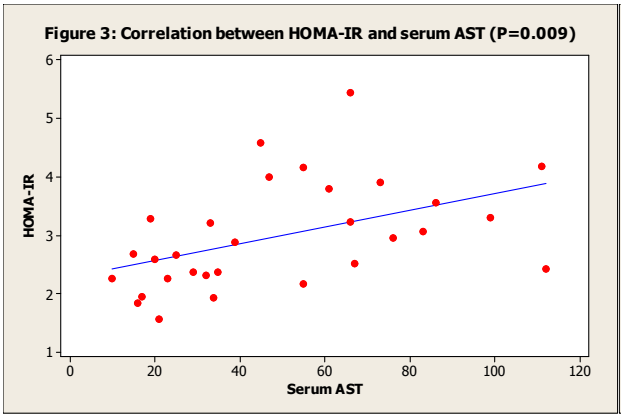
Table 3 shows that, in group 1, there was highly significant correlation between serum iron and both ALT and AST *(p<0.01)*. TSAT had a significant correlation only with ALT *(p<0.05)* but not with AST *(p>0.05)*.

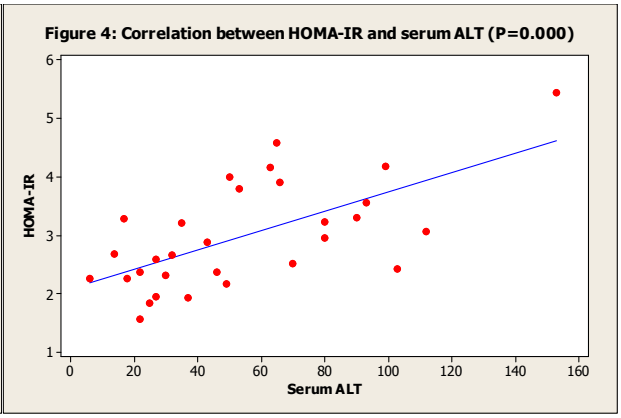
Table 3: Correlation of serum iron and TSAT to serum transaminases (ALT and AST) in Group 1

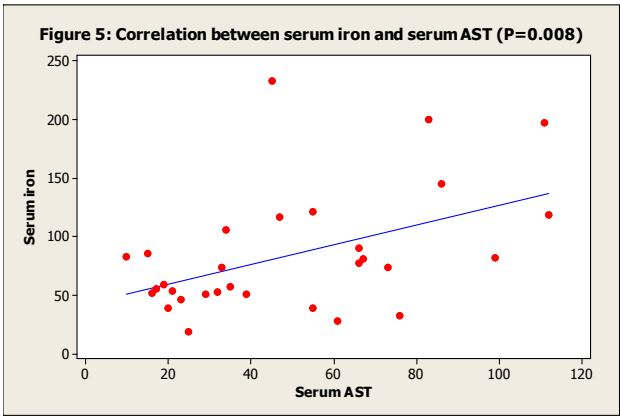
	Iron		TSAT	
	r	p	r	p
AST	**0.476**	**0.008**	**0.340**	**0.066**
ALT	**0.486**	**0.007**	**0.410**	**0.024**

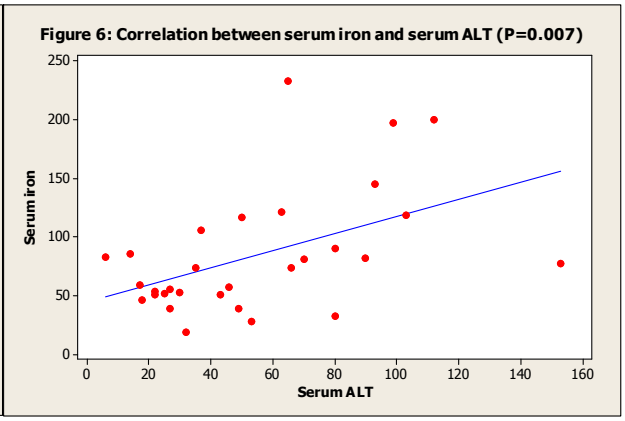












4. Discussion

In our cross sectional observational study, 60 non-diabetic patients on chronic hemodialysis in Ain Shams university hospital were chosen and divided into 2 groups, **group 1** consisted of 30 HCV seropositive cases and **group 2** consisted of 30 HCV seronegative cases.

Comparing group 1(HCV+ve) to group 2 (HCV-ve), we found that HCV positive cases had a longer duration on dialysis more than HCV negative cases *(P<0.001).*This result agrees with most of researches done in this field including the CDC which stated that the duration on dialysis is the major risk factor independently associated with high rates of HCV infection due to multiple exposure to nosocomial transmission of HCV***(11).***A relatively large study in Brazil demonstrated that patients on hemodialysis for more than 3 years had a 13.6-fold greater risk of HCV positivity compared to subjects with less than one year hemodialysis treatment***(12).***

In our study we found that the incidence of insulin resistance was 86.67% in group 1 (26 cases) while in group 2 the incidence was 33.33% (10 cases). Pearson chi square test detected that the incidence of IR was significantly higher in HCV seropositive cases than in HCV seronegative cases *(p<0.05).* The overall incidence of IR in both groups was 36 cases (72%).**Ali et al, *(13)***found that the incidence of IR in HCV+ve cases on hemodialysis was 64.7% but he used a cutoff point of>2.5 which was higher than our cutoff point of >2.**Sit et al,** also agreed with us and found the overall incidence to be 68.4% after exclusion of diabetic and obese patients ***(14).***However, these findings prove that HCV infection is closely linked to the development of IR in hemodialysis patients rendering them at risk of IR complications.

Comparing group 1 to group 2, there was insignificant difference as regards FBS *(p>0.05)* but fasting insulin was significantly higher *(p<0.001)*in HCV +ve cases denoting that IR was on the account of fasting insulin. So, we conclude that fasting insulin alone is sufficient as a measure of insulin resistance in non- diabetic patients on chronic hemodialysis. Our results coincide with **Ali et al,** who stated the same ***(13).***

Hemoglobin was found to be significantly higher in seropositive group than in seronegative patients *(p=0.001).* Our results agree with **Sahin et al.,** and **Elsaran et al, *(15)(16).***In HCV infection, there is increased production of hepatic erythropoietin ***(15).*****Sabry et al,** found insignificant

difference of hemoglobin in seropositive and seronegative patients on hemodialysis but they found that, seropositive cases need lower doses of EPO therapy to attain >adequate hemoglobin levels. They attributed their results to the difference in demography of patients, different genotype of the HCV virus, different dialysis durations and inadequate iron supply ***(17).***

AST and ALT were significantly higher (*p=0.001* for AST and *p<0.001* for ALT) in HCV+ve group indicating the activity of HCV. There was a highly significant correlation between HOMA-IR and both AST *(p<0.01)* and ALT *(p<0.001)* in group 1. The mechanism by which HCV infection induces IR is through an inflammatory process which increases the oxidative stress. Oxidative stress, in HCV-infected patients, has been shown to correlate with IR, independent of obesity ***(18).*** This may imply a role for antioxidants as a protective therapy ***(19).*****Ali et al,** found the same relationship between HOMA-IR and ALT and stated that high ALT levels seen in HCV+ve chronic hemodialysis patients can indicate hyperinsulinemia, as well as HCV infection ***(13).*****Anthony et al,** concluded that ALT was associated with insulin resistance independently of conventional and more detailed metabolic measures. These findings suggest that the addition of ALT to existing clinically based metabolic risk definitions is an inexpensive way to improve the identification of subjects with insulin resistance ***(20).***

Iron overload has been found to reduce the hepatic metabolism of insulin leading to hyperinsulinemia ***(21).*** This process can lead to redistribution of transferrin receptors on the cell surface and stimulation of more iron uptake by the liver ***(22).*** In our study, serum iron *(p<0.01),* serum ferritin *(p<0.05)* and TSAT *(p<0.05)* were significantly higher in HCV seropositive patients than in seronegative patients. P value was more significant in case of iron and TSAT than in case of serum ferritin. This could be explained by the fact that ferritin is an acute phase reactant which might increase in any inflammatory response or in ESRD itself with or without insulin resistance ***(23)(24).*** This fact, also, can explain why insulin resistance did not correlated significantly to serum ferritin*(p>0.05)* while there was a highly significant correlation between IR and both serum iron*(p<0.01)* and TSAT*(p<0.01)* (table 2).In our study, we found a significant correlation between serum iron and both ALT*(p<0.01)* and AST *(p<0.01).*Previous study has been performed, showing an association between increased serum ferritin and serum ALT***(25).***We suggest a complexion of increased serum iron and aminotransferases (ALT and AST) to be an associate of insulin resistance in HCV infected patients on chronic hemodialysis.

In conclusion, it was observed that using HOMA-IR at a cutoff point of >2, the prevalence of IR in HCV +ve cases on chronic hemodialysis was 86.67% and was 33.33% in HCV-ve cases. Severity of insulin resistance is proportional to the activity of HCV marked by AST and ALT. Serum iron and TSAT are better predictors of insulin resistance than serum ferritin. There is a close relationship between serum iron and (ALT and AST) that might be a complex associate of insulin resistance in HCV +ve cases on chronic hemodialysis.

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