The Effect of Hepatitis C Virus Infection on Insulin Resistance in Chronic Hemodialysis Patients

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Introduction

İt is well known that HCV infection has many extra-hepatic manifestations including type 2 diabetes mellitus (DM) caused by autoimmun and non-autoimmun mechanisms (1-3). A link between chronic HCV infection and type 2 DM is supported by the facts that type 2 DM is seen 2-5 times more frequent at patients with HCV-related liver diseases and HCV is 2-5 times more prevalent at type 2 diabetic patients (4-6). The higher prevalence of type 2 DM at HCV (+) patients is not related exclusively to cirrhosis (4). HCV infection is closely linked with type 2 DM, but the pathogenetic mechanism is still obscure (3,7). Patients with chronic renal failure often have disorders of carbonhydrate metabolism and insulin resistance as well as HCV infection (8). The contribution of HCV infection to insulin resistance is expected at patients with chronic renal failure ; and as far as we know there have not been any researches done about this matter. In this study, the probable relation between HCV infection and insulin resistance as welll as some of the parameters associated with insulin resistance is evaluated at patients on haemodialysis therapy.

Materials and Methods

This study has been performed with 55 patients who were on haemodialysis therapy regularly three times a week. 34 of them were HCV (+) (20 females and 14 males; aged 17-72 years, mean 40,94±17,06; mean BMI: 20,5±3 kg/m^2) and 21 of them were negative for HCV and other viral markers (8 females and 11 males; aged 17-80, mean 52,62±20,64; mean BMI: 22±4 kg/m^2). Patients who were negative for HCV and other viral markers were defined shortly as the HCV (-) group. Insulin resistance was calculated according to the Homeostasis model assessment (HOMA) formula (9,10): fasting insulin (mU/L) x fasting glucose (mmol/L) / 22,5. Patients were called HOMA İR (+) if their HOMA insulin resistance scores were ≥2,5. All the HOMA-İR (+) patients in both groups were called as HOMA-İR (+) subgroup. The control group was formed with 9 healthy subjects to compare their insulin and C-peptide levels with the patients. Insulin, C-peptide and glucose levels were studied at three different venous serum samples taken with intervals of 5 minutes after 12 hours of fasting.

Subjects with histories of corticosteroid use, pancreatic diseases, advanced liver diseases or cirrhosis were excluded from the study. Patients with repeated fasting venous serum glucose levels <110 mg/dl were recruited for the study. All patients were taking parenteral iron, erythropoietin, calcium acetate, calcium carbonate and active vitamin D_3 preparations according to periodic controls of hemogram, iron parameters and calcium-phosphorus levels.

Insulin level was measured with Hitachi Modula E170 machine (Elecsys insulin kit No: 12017547). C-peptide levels were examined with immodulate machine (kit 254 R 13T11 code). Serum levels of some parameters accompanying insulin resistance such as triglyceride, ferritin, fasting glucose, Mg, ALT, iPTH, and ages of the patients were also analyzed.

Statistical analyses were conducted by using SPSS (Statistical Package for Social Sciences) for windows 10.0 program. Results were expressed as means±SD. Comparisons between groups were made using Student's T-test, Mann-Whitney U test, X^2 or Fisher exact probability test for appropriate data. Simple (Pearson) correlation coefficients between HOMA-İR and measures of variables were calculated. Probability levels less than 0,05 were considered significant.

Results

There were no significant differences in body mass index and sex between HCV (+) and HCV (-) groups.

IR was described according to HOMA formula in 22 of 34 HCV (+) (64,7%) and 7 of 21 HCV (-) subjects (33,33%) (Qui square=5,126, p=0,024<0,05).

Insulin levels of HCV (+) patients were significantly higher than both HCV (-) and the control groups (6,40±4,94) (p<0,05). C-peptide levels of HCV (+) and HCV (-) subjects were significantly higher than that of the control group (2,36±1,56) (p<0,001).

Results of insulin, C-peptide, HOMA score and serum levels of some parameters accompanying insulin resistance at HCV (+) and (-) groups and HOMA İR (+) and (-) subgroups were shown at table-1 and 2.

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Table I : Statistical results of biochemical parameters at HOMA-IR (+) and (-) subjects in HCV (+) and HCV (-) groups

		HOMAİR (+)	HOMAİR(-)	P
HCV(+)	Yaş	40,86±17,55	40,92±16,71	0,993
	İnsülin	17,74±8,98	5,23±1,69	0,000
	C-Peptide	8,06±2,62	6,46±2,39	0,149
	HOMA score	3,83±2,27	0,94±0,29	0,000
	Fasting Glucose	86,45±14,89	74,25±10,86	0,016
	ALT	25,50±20,84	21,5±10,78	0,971
	Triglyceride	166,27±68,45	124,83±56,08	0,084
	Ferritin	687,95±484,8	680,51±644,22	0,493
	İPTH	482,14±353,58	342,25±141,16	0,264
	Mg	2,97±0,43	3,03±0,36	0,572
HCV(-)	Yaş	52,00±23,25	52,93±20,14	0,926
	İnsülin	18,04±5,81	4,59±1,84	0,000
	C-Peptide	7,07±2,79	8,28±3,41	0,582
	HOMA score	3,84±1,35	0,91±0,41	0,000
	Fasting Glucose	87,29±13,61	80,86±12,82	0,262
	ALT	14,14±7,99	14,79±7,09	0,793
	Triglyceride	156,43±57,90	117,71±42,65	0,079
	Ferritin	491,5±154,39	483,65±448,85	0,293
	İPTH	256,00±97,8	279,95±212,86	1
	Mg	3,01±0,51	2,32±0,48	0,351

Table II : Biochemical parameters of HCV (+) and HCV (-) groups

	HCV(+)	HCV (-)	P
Yaş	40,94±17,06	52,62±20,64	0,027
İnsülin	13,32±9,44	9,07±7,39	0,039
C-Peptide	7,6±2,62	8,12±3,15	0,742
HOMA score	3,83±2,27	3,84±1,35	0,646
Fasting Glucose	82,15±14,68	83,0±13,11	0,862
ALT	24,09±17,86	14,57±7,21	0,003
Triglyceride	151,65±66,59	130,62±50,38	0,267
Ferritin	685,33±536,58	486,60±375,73	0,191
İPTH	432,76±301,34	271,97±179,63	0,034
Mg	2,99±0,40	2,88±0,49	0,322

Significant positive correlations were found between age-insulin (r=0,456, p=0,049), age-C-peptide (r=0,654, p=0,002); HOMA score-glucose (r= 0,958, p<0,001), HOMA score-insulin)r=0,432; p<0,05; ALT and insulin levels(r=0,374, p=0,045) while there were significant negative correlations between age-Mg and age-iPTH levels (r= -0,547 p=0,003) at HOMA İR (+) HCV (+) patients. Insignificant negative correlations were found between Mg- C-peptide (r=-0,327, p=0,171), Mg-insulin (r= -0,168; p=0,490) and Mg-triglyceride (r=-0,381, p=0,107), iPTH-insulin and iPTH-C-peptide levels.

Discussion

Together with many other factors uremia affects the carbonhydrate metabolism and insulin resistance. On the other hand, insulin resistance and hyperinsulinemia are important risk factors for atherosclerosis and death due to cardiovascular reasons at about 50% of patients with chronic renal failure (11). HOMA formula which is used large scaled investigations to measure insulin resistance is suitable also for patients with chronic renal failure (12). This study was planned to show the relation between HCV and insulin resistance at chronic haemodialysis patients and insulin resistance was found significantly higher (p<0.05) at HCV (+) patients suggesting that HCV infection affects insulin resistance independent of uremia.

It is not easy to predict whether type 2 DM or HCV infection develops earlier because both of these diseases have insidious onsets (2,3). At haemodialysis patients HCV infection is usually acquired later, therefore, it can be suggested that insulin resistance follows HCV infection.

At general population elder age is risk factor for insulin resistance. In this study, significant positive correlations were found between age-insulin and age-C-peptide. HCV's contribition to insulin resistance becomes clearer when we pay attention to the finding that HCV (+) patients are younger.

Serum insulin level alone can be a good marker for insulin resistance (13). The results of this study show that HCV (+) chronic haemodialysis patients have higher insulin levels than normal and HCV (-) population and a positive correlation was found between HOMA score and insulin level independent of uremia. Serum insulin level may be a good indicator for insulin resistance also for haemodialysis patients.

C-peptide is a marker of endogenous insulin secretion and patients with chronic renal failure have high levels of c-peptide. Kidney is the major site for c-peptide metabolism and c-peptide levels are six times higher at nephrectomized patients (14). In our study, it is shown that haemodialysis patients have significantly higher c-peptide levels than the control group. The high c-peptide level found in this study was probably due to reduced metabolism since no significant correlation was observed among c-peptide and HOMA score in any of the groups. When high c-peptide level is considered together with high insulin level, impaired carbohydrate metabolism seen in patients with chronic renal failure including HCV(+) ones can be related to peripheral resistance rather than insufficient insulin secretion.

Fasting glucose level is another parameter associated with insulin resistance (13). In this study, HOMA-İR (+) subjects had higher glucose levels than HOMA-İR(-) subjects in HCV(+) group and a positive correlation was found between HOMA score and fasting glucose in HOMA-İR(+) subgroup. High serum glucose levels seen in HCV(+) chronic haemodialysis patients can be related with insulin resistance.

Usually ALT levels are used for the screening for hepatitis C at chronic haemodialysis patients (15). Patients with end stage renal failure have low ALT activity compared with general population (16). High ALT activity may be an indicator of insulin resistance (13). In this study, a positive correlation between insulin level and ALT level was shown at all HOMA IR(+) patients. Therefore, high ALT levels seen at HCV(+) chronic haemodialysis patients can indicate hyperinsulinemia as well as HCV infection.

Many studies show a positive correlation among insulin resistance and triglyceride, ferritin, iPTH and Mg levels (6, 17-23). In this study, no significant correlation was found between these parameters and HOMA score. No significant

correlation was found between HOMA score and ferritin and iPTH levels in this study and this may be because that this study was performed with patients who regularly got parenteral iron and erythropoietin, calcium acetate, calcium carbonate and active vitamin D_3 preparations according to their needs. Erythropoietin treatment improves insulin resistance as well as anemia. Another important finding in this study is that there was negative correlation between iPTH and age at all HOMA IR(+) patients. Parathormon levels usually get higher by age , but at patients with chronic renal failure elder age is a risk factor for adynamic bone diseases. 25% of the patients included in this study were over 64.

Conclusion

1. This study shows that:
2. HCV infection is related with insulin resistance, insulin and glucose levels independent of other factors,
3. Chronic haemodialysis patients have high c-peptide levels,
4. High levels of ALT may indicate hyperinsulinemia as well as HCV infection at HCV(+) chronic haemodialysis patients,
5. Elder age may have an effect on insulin resistance at haemodialysis patients as well as general population.
6. Contribution of HCV infection to cardiovascular mortality at patients with chronic renal failure is worth to consider.

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