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Renal function is impaired in normotensive chronic HCV patients: role of insulin resistance

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Abstract Renal dysfunction is an independent predictor for cardiovascular morbidity and mortality. We investigated whether chronic hepatitis C virus (HCV) infection and the related insulin resistance/hyperinsulinemia influence renal function in comparison with a group of healthy subjects and with another group with metabolic syndrome. We enrolled 130 newly diagnosed HCV outpatients matched for age and gender with 130 patients with metabolic syndrome and 130 healthy subjects. Renal function was evaluated by calculation of glomerular filtration rate (e-GFR, mL/min/1.73 m^2) using the CKD-EPI equation. The following laboratory parameters were measured: fasting plasma glucose and insulin, total, LDL- and HDL-cholesterol, triglyceride, creatinine, and HOMA to evaluate insulin sensitivity. HCV patients with respect to both healthy subjects and metabolic syndrome patients have a decreased e-GFR: 86.6 ± 16.1 vs 120.2 ± 23.1 mL/min/1.73 m^2 ($P < 0.0001$) and 94.9 ± 22.6 mL/min/1.73 m^2 ($P = 0.003$), respectively. Regarding biochemical variables, HCV patients, in comparison with healthy subjects, have a higher triglyceride level, creatinine, fasting insulin and HOMA (3.4 ± 1.4 vs 2.6 ± 1.3; $P < 0.0001$). At linear regression analysis, the correlation between e-GFR and HOMA is similar in the metabolic syndrome ($r = -0.555$, $P < 0.0001$) and HCV ($r = -0.527$, $P < 0.0001$) groups. At multiple regression analysis, HOMA is the major determinant of e-GFR in both groups, accounting for, respectively, 30.8 and 27.8 % of its variation in the metabolic syndrome and HCV. In conclusion, we demonstrate that HCV patients have a significant reduction of e-GFR and that insulin resistance is the major predictor of renal dysfunction.

Keywords Chronic C hepatitis · Renal function · Insulin resistance · Cardiovascular risk · Metabolic syndrome

Introduction

Chronic hepatitis C virus (HCV) infection is associated with several metabolic alterations that contribute to development of subclinical cardiovascular disease, particularly atherosclerotic vascular damage [1–4]. In accordance with this, we recently demonstrate that hyperinsulinemia HCV-related is associated with both increased cardiac mass and arterial vascular stiffness, that are considered independent and strong predictors of cardiovascular events also in different settings of patients [5–8].

In addition, the metabolic syndrome (MS), characterized by visceral obesity and insulin resistance (IR), is associated with a decrease in renal function that also represents an independent and strong predictor of cardiovascular morbidity and mortality in the general population [9, 10]. In

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particular, the National Health and Nutrition Examination Survey (NHANES) III, demonstrates a strong association between the MS and the development of chronic kidney disease (CKD); while, data reported by the Atherosclerosis Risk in Communities Study (ARIC) demonstrates a strong correlation between IR status and loss of renal function [11, 12].

On the other hand, there is conflicting evidence about the possible association between HCV infection and CKD; particularly, the majority of these studies fail to show an association between these two clinical conditions [13–16]. Taken together, the aim of this study was to evaluate the possible association between chronic HCV infection-related IR and renal dysfunction in comparison with both healthy subjects and MS patients.

Methods

Study population

For this aim, we designed a cross-sectional study involving patients evaluated at the University Hospital of Catanzaro. We recruited 130 HCV^+ normotensive Caucasian outpatients (75 males and 55 females, mean age 55.2 ± 13.9 years). They were matched for age and gender in a 1:1:1 ratio with 260 subjects participating in the CAtanzaro MEtabolic RIsk factors Study (CATAMERIS), with 130 patients with MS (mean age 54.6 ± 10.3 years) evaluated according NCEP-ATP III criteria [17] and 130 healthy subjects (mean age 54.4 ± 11.9 years) [18]. At the time of the first evaluation, both HCV^+ and MS patients were newly diagnosed and untreated with antiviral therapy or other drugs. In the whole study population, exclusion criteria were type 2 diabetes (T2D) detected by an oral glucose tolerance test, according to ADA guidelines; history or clinical evidence of previous cardiovascular events, administration of any drugs interfering with glucose metabolism or renal function; kidney, thyroid, endocrine and advanced liver diseases, transplanted patients, history of malignant disease; history of chronic abuse of alcohol (>40 g/die) or recreational drugs. None of HCV patients had liver cirrhosis, detected by clinical and ultrasound examinations. In addition, in these patients we excluded membranoproliferative glomerulonephritis by 24-h proteinuria and cryoglobulinemia.

We performed measurements of height and weight according to a standardized protocol, and body mass index (BMI) was calculated as kilograms per square meter. The Ethics Committee approved the protocol and informed written consent was obtained from all participants. All the investigations were performed in accordance with the principles of the Declaration of Helsinki.

Blood pressure measurements

Readings of clinic blood pressure (BP) were obtained in the left arm of the supine patients, after 5 min of quiet rest, with a mercury sphygmomanometer. A minimum of three BP readings were taken on three separate occasions at least 2 weeks apart. Systolic and diastolic BP were recorded at the first appearance (phase I) and the disappearance (phase V) of Korotkoff sounds. Baseline BP values were the average of the last two of the three consecutive measurements obtained at intervals of 3 min. Patients with a clinic systolic BP (SBP) <130 mmHg and diastolic BP (DBP) <80 mmHg were defined as normotensives.

Laboratory determinations

All laboratory measurements were performed after 12 h of fasting. Plasma glucose was determined immediately by the glucose oxidation method [Glucose analyzer, Beckman Coulter, Milan; intra-assay coefficient of variation (CV) 2.2 %, inter-assay CV 3.8 %]. Serum insulin was determined in duplicate by a highly specific radioimmunoassay using two monoclonal antibodies; intra-assay CV 2.1 %, inter-assay CV 2.9 %. Total, low-density lipoprotein- (LDL), and high-density lipoprotein- (HDL) cholesterol and triglyceride concentrations were measured by enzymatic methods (Roche Diagnostics GmbH, Mannheim, Germany). Quantitative HCV-RNA was assayed by a real-time polymerase chain reaction assay.

Insulin resistance evaluation

IR was estimated by homeostasis model assessment (HOMA) according to the following equation: HOMA = [insulin (μU/ml × glucose (mmol/l)]/22.5 [19].

Renal function evaluation

Creatinine was measured by using Jaffe methodology. Values of estimated glomerular filtration rate (e-GFR, mL/min/1.73 m^2) were calculated by using the equation proposed by investigators in the chronic kidney disease epidemiology (CKD-EPI) collaboration [20].

Statistical analysis

ANOVA for continuous clinical and biological data was performed to test the differences among groups, and the Bonferroni post hoc test for multiple comparisons was further performed; for dichotomic variables we used the X^2 test. Data are expressed as mean ± SD, and binary data as percent frequency. Linear regression analysis was performed to correlate e-GFR with the following covariates:

age, BMI, waist, SBP, DBP, pulse pressure (PP), LDL- and HDL-cholesterol, triglyceride, fasting plasma glucose and insulin, HOMA and uric acid. Subsequently, to define the independent predictors of renal function, variables reaching statistical significance, were inserted in a stepwise multivariate linear regression model. In this one, to avoid a possible colinearity, we did not include age, fasting glucose and insulin, but we considered only HOMA. Correlational analysis was performed in the whole study population and in the three groups separately. Differences were assumed to be significant at $P < 0.05$. All calculations were done with a standard statistical package (SPSS for Windows version 20.0, Chicago, IL, USA).

Results

Study population

Clinical and laboratory characteristics of the study population are reported in Table 1. There were no significant differences among groups for age, gender, smoking and heart rate. Of interest, HCV^+ patients, with respect to both healthy and MS subjects show a lower and significant ($P < 0.0001$) e-GFR (Fig. 1). In addition, regarding other biochemical variables, HCV^+ patients, in comparison with healthy subjects, have higher triglyceride level, creatinine, fasting insulin and HOMA, and lower BMI, total and HDL-cholesterol.

On the contrary, HCV^+ patients in comparison with the MS group have a lower BMI, waist circumference, systolic and diastolic BP, cholesterol, triglyceride, and fasting glucose. Of interest, no significant differences are found in fasting insulin and HOMA values (3.7 ± 1.4 vs 3.4 ± 1.4; $P = 0.287$).

In HCV^+ patients the mean value of HCV-RNA was $3579 \pm 1710 \times 10^3$ (UI/ml).

Correlational analysis

A linear regression analysis was performed to test the correlation between e-GFR and different covariates in the whole study population and in the three groups separately (Table 2). In the whole study population, e-GFR is significantly correlated with HDL-cholesterol and inversely with age, waist circumference, SBP, DBP, PP, triglyceride, fasting glucose, insulin, HOMA and uric acid. In the MS and HCV^+ groups, e-GFR is statistically correlated with age, waist circumference, HDL cholesterol, uric acid, fasting glucose, insulin and HOMA. In addition, in the MS group, the other covariates that correlate with e-GFR are: SBP and pulse pressure.

A stepwise multivariate linear regression analysis was performed to evaluate the independent predictors of e-GFR in the entire population and in the three different groups (Table 3). In the whole population, as well as in MS and HCV^+ groups, HOMA is the major predictor of e-GFR, accounting for 25.8, 30.8 and 27.8 % of its variation, respectively. Of interest, 1 unit of HOMA increase produces a reduction of -6.062 ml/min/1.73 m^2 in MS group and of -3.155 ml/min/1.73 m^2 in HCV^+ patients. In the whole population, other independent predictors of e-GFR are HDL cholesterol, uric acid and waist circumference, accounting for, respectively, another 9.4, 3.5 and 1.2 % of its variation. In the MS group, the other covariates retained in the model are uric acid, waist circumference, gender and HDL cholesterol accounting for, respectively, 10.3, 5.4, 4.3 and 2.4 % of e-GFR variation. In the HCV^+ group, covariates retained in the final model are gender, waist circumference, uric acid and HDL cholesterol accounting for, respectively, another 11.6, 10.5, 2.6 and 1.6 % of its variation.

Discussion

The results of this study demonstrate that HCV^+ patients, in comparison with healthy subjects and MS patients, have a significant decrease in e-GFR. These results have a clinical relevance because they help to clarify the pathogenetic role of HCV infection in promoting renal damage in a group of newly diagnosed HCV^+ patients without membranoproliferative glomerulonephritis or cryoglobulinemia, all established factors affecting renal function in this clinical setting. Contrary to other previously published studies, aimed at demonstrating an association between HCV infection and CKD, our data emphasize the early role of viral infection on renal function decrease, also in patients with still preserved renal function; this condition has a clinical relevance because it should alert physicians to routinely evaluate renal function in these patients [13–16, 21, 22]. Thus, on the basis of this evidence, we hypothesize that early detection of a loss of renal function may be useful in slowing the progression to CKD by appropriate therapeutic interventions. The large sample size and detailed characterization of patients confer to our study a very important clinical and biological plausibility that contributes to clarify the association between HCV infection and reduction of renal function, similar to that observed for other subclinical organ damages [5, 6].

Another important finding obtained by our study consists in the fact that IR is a primary and independent predictor of e-GFR variation in both HCV^+ and MS patients, as already reported [11, 12]. The interaction between metabolic and hemodynamic parameters may be explained

Table 1 Demographic, clinical and humoral characteristics of the whole study population and the three groups separately

	All ($n = 390$)	Healthy ($n = 130$)	MS ($n = 130$)	HCV^+ ($n = 130$)	*P*	MS vs H[a]	HCV^+ vs N[a]	HCV^+ vs MS[a]
Age, years	54.7 ± 12.1	54.4 ± 11.9	54.6 ± 10.3	55.2 ± 13.9	0.870	0.999	0.999	0.999
Sex, M/F	225/165	75/55	75/55	75/55	0.999[b]	0.999[b]	0.999[b]	0.999[b]
BMI, Kg/m^2	28.3 ± 4.4	28.3 ± 4.7	30.8 ± 3.7	25.8 ± 3.2	<0.0001	<0.0001	<0.0001	<0.0001
Waist, cm	95.1 ± 12.2	90.4 ± 12.3	103.8 ± 10.9	91.1 ± 8.3	<0.0001	<0.0001	0.999	<0.0001
Current smokers, *n* (%)	83 (21.3)	22 (16.9)	27 (20.8)	34 (26.1)	0.189[b]	0.526[b]	0.097[b]	0.380[b]
Systolic BP, mmHg	131.6 ± 17.6	124.5 ± 12.5	147.9 ± 16.6	122.4 ± 9.8	<0.0001	<0.0001	0.571	<0.0001
Diastolic BP, mmHg	81.9 ± 11.9	76.9 ± 8.2	92.1 ± 11.2	76.9 ± 8.1	<0.0001	<0.0001	0.999	<0.0001
Heart rate, bpm	68.7 ± 8.7	69.1 ± 10.2	69.1 ± 7.9	68.2 ± 7.6	0.682	0.999	0.999	0.999
Total cholesterol, mg/dl	188.7 ± 35.2	189.1 ± 32.1	204.1 ± 33.7	173.1 ± 32.9	<0.0001	0.001	<0.0001	<0.0001
LDL-cholesterol, mg/dl	120.3 ± 32.8	117.5 ± 29.9	131.7 ± 34.8	118.3 ± 34.7	<0.0001	0.001	0.425	<0.0001
HDL-cholesterol, mg/dl	43.5 ± 10.1	48.4 ± 9.9	44.3 ± 10.6	37.9 ± 6.4	<0.0001	0.001	<0.0001	<0.0001
Triglyceride, mg/dl	126.8 ± 57.2	115.1 ± 42.9	148.6 ± 46.8	130.2 ± 39.3	<0.0001	<0.0001	0.015	0.002
AST, U/l	34.8 ± 14.2	18.7 ± 5.1	41.5 ± 17.6	45.5 ± 17.8	<0.0001	<0.0001	<0.0001	0.073
ALT, U/l	37.1 ± 15.1	22.9 ± 4.8	43.6 ± 18.7	46.1 ± 18.3	<0.0001	<0.0001	<0.0001	0.277
Uric acid, mg/dl	5.1 ± 1.2	4.9 ± 1.0	5.3 ± 1.2	5.1 ± 1.2	0.032	0.028	0.331	0.928
Creatinine, mg/dl	0.8 ± 0.2	0.8 ± 0.1	0.9 ± 0.2	0.9 ± 0.1	<0.0001	<0.0001	<0.0001	0.338
e-GFR, ml/min/1.73 m^2	98.7 ± 24.3	120.2 ± 23.1	94.9 ± 22.6	86.6 ± 16.1	<0.0001	<0.0001	<0.0001	0.003
Fasting glucose, mg/dl	96.5 ± 11.6	92.3 ± 10.2	101.8 ± 11.4	95.4 ± 11.1	<0.0001	<0.0001	0.059	<0.0001
Fasting insulin, μU/ml	13.6 ± 5.6	11.5 ± 5.3	14.8 ± 5.4	14.6 ± 5.6	<0.0001	<0.0001	<0.0001	0.999
HOMA	3.3 ± 1.4	2.6 ± 1.3	3.7 ± 1.4	3.4 ± 1.4	<0.0001	<0.0001	<0.0001	0.287

BMI body mass index, *BP* blood pressure, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *e-GFR* estimated glomerular filtration rate, *HOMA* homeostasis model assessment

[a] By Bonferroni post hoc test

[b] Chi-square test

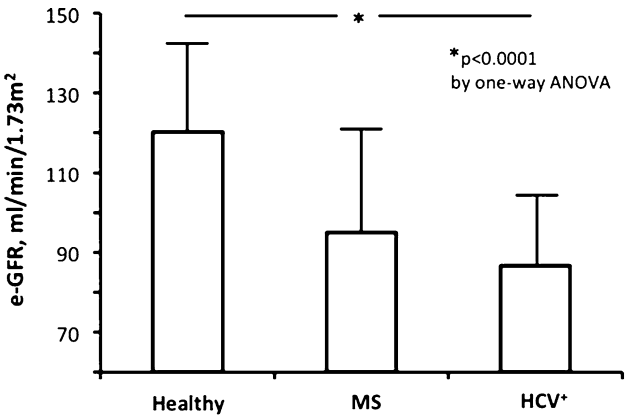

Fig. 1 We graphically reported estimated glomerular filtration rate (e-GFR) mean values in all three different study groups. HCV^+ patients presented a significantly lower e-GFR in comparison with both healthy subjects and metabolic syndrome (MS) patients ($P < 0.0001$, by ANOVA)

by previously published data demonstrating that functional GFR reduction is inversely related to circulating IGF-1 levels [23]. In fact, there is evidence that low IGF-1 levels impair vasodilating properties of renal arterioles that decrease both renal blood flow and GFR. This evidence is explained by our and other data demonstrating that a dynamic balance exists between IR-related hyperinsulinemia and IGF-1 levels [24–26]. In accordance with this, it is clearly demonstrated that endogenous IGF-1 levels improve GFR by stimulating the glomerular L-arginine-nitric oxide pathway, without any systemic hemodynamic changes [27, 28].

It is well established that visceral obesity is characterized by an IR status; in fact, there is growing evidence demonstrating that a selective excess of visceral adipose tissue is associated with a higher risk to develop IR because it acts as an endocrine organ that produces several substances involved in the regulation of metabolic, inflammatory and immune responses [29, 30]. In keeping with this, it is not surprising that MS patients develop an IR that may be considered the common soil for metabolic and hemodynamic alterations that produce the definition of this syndrome, and that may promote the associated target organ damage. In accordance with this, the presence of a MS entails a twofold increased risk for microalbuminuria, an early indicator of renal damage [31]. In HCV^+ patients, it has been demonstrated that the IR degree may be explained through a direct interaction between viral products and the insulin signaling pathway via IRS-1-PI3-kinase-Akt [32–34]. The biological plausibility of this finding is also supported by the present results demonstrating that HOMA is the major determinant of e-GFR decrease in MS and HCV^+ patients, accounting for 30.8 and 27.8 % of its variation, respectively. In addition, HCV^+ patients, in comparison with healthy subjects, while presenting a significant lower BMI, show an increased, although not significant, waist circumference. This is the second independent predictor of e-GFR accounting for 10.5 % of its variation.

Interestingly, all these conditions interact between them in promoting the e-GFR reduction with important clinical implications, considering that the loss of renal function is an independent predictor of cardiovascular morbidity and mortality [9, 10]. For these reasons CKD is a relevant health problem not only in the specific setting of patients but also in the general population..

Table 2 Linear regression analysis between e-GFR and different covariates in the whole study population and in the three groups

	All ($n = 390$)		Healthy ($n = 130$)		MS ($n = 130$)		HCV^+ ($n = 130$)	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age, years	−0.265	<0.0001	−0.257	0.002	−0.196	0.013	−0.516	<0.0001
BMI, kg/m^2	0.038	0.230	−0.055	0.267	−0.027	0.379	0.008	0.465
Waist, cm	−0.283	<0.0001	−0.147	0.048	−0.351	<0.0001	−0.380	<0.0001
Systolic BP, mmHg	−0.167	<0.0001	−0.0201	0.410	−0.328	<0.0001	0.043	0.313
Diastolic BP, mmHg	−0.094	0.032	−0.014	0.438	0.037	0.336	−0.033	0.356
PP, mmHg	−0.146	0.002	−0.013	0.440	−0.389	<0.0001	0.080	0.183
LDL Cholesterol, mg/dl	−0.081	0.055	−0.342	<0.0001	−0.080	0.182	0.090	0.153
HDL Cholesterol, mg/dl	0.433	<0.0001	0.144	0.052	0.384	<0.0001	0.341	<0.0001
Triglyceride, mg/dl	−0.137	0.003	−0.099	0.132	−0.001	0.494	0.049	0.289
Fasting glucose, mg/dl	−0.294	<0.0001	−0.119	0.089	−0.279	0.001	−0.340	<0.0001
Fasting insulin, μUI/ml	−0.468	<0.0001	−0.259	0.001	−0.514	<0.0001	−0.472	<0.0001
HOMA	−0.508	<0.0001	−0.273	0.001	−0.555	<0.0001	−0.527	<0.0001
Uric acid, mg/dl	−0.360	<0.0001	−0.266	0.001	−0.444	<0.0001	−0.407	<0.0001

MS metabolic syndrome, *BMI* body mass index, *BP* blood pressure, *PP* pulse pressure, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *e-GFR* estimated glomerular filtration rate, *HOMA* homeostasis model assessment

Table 3 Stepwise multiple regression analysis on e-GFR, as dependent variable in whole study population and in the three groups (not including age, fasting glucose and insulin, pulse pressure when significant to avoid colinearity)

	All ($n = 390$)		Healthy ($n = 130$)		MS ($n = 130$)		HCV^+ ($n = 130$)	
	Partial R^2 (%)	P	Partial R^2 (%)	P	Partial R^2 (%)	P	Partial R^2 (%)	P
HOMA	25.8	<0.0001	6.5	0.001	30.8	<0.0001	27.8	<0.0001
HDL cholesterol, mg/dl	9.4	<0.0001	–	–	2.5	0.011	1.6	0.037
Uric acid, mg/dl	3.5	<0.0001	2.2	0.049	10.3	<0.0001	2.6	0.010
Waist, cm	1.2	0.005	–	–	5.4	<0.0001	10.5	<0.0001
LDL cholesterol, mg/dl	–	–	8.7	<0.0001	–	–	–	–
Gender, male/female	–	–	12.4	<0.0001	4.0	0.002	11.6	<0.0001
Smoking, yes/no	–	–	2.5	0.035	–	–	–	–
Total R^2 (%)	39.9	–	32.3	–	51.0	–	54.1	–

MS metabolic syndrome, *e-GFR* estimated glomerular filtration rate, *HOMA* homeostasis model assessment

Study limitation

These data are associative, and do not definitively support regarding the role of metabolic alterations in promoting renal dysfunction.

Recently, new drugs are reported to be able to counteract HCV replication and limit the progression of liver disease with a high likelihood of healing. However, at this moment, no data are available regarding the impact of microbiological healing on extrahepatic clinical manifestations, which contribute to morbidity and mortality in these patients.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Written informed consent was obtained from all participants.

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