THE RISK OF CARDIOVASCULAR DISEASE IN A COHORT OF CHRONIC HEPATITIS C PATIENTS

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ABSTRACT

Background. The idea of a relationship between HCV infection and host lipid and glucid homeostasis is widely accepted, with an impact on liver disease progression. However, the association between HCV infection and cardiovascular (CV) risk is controversial.
Aim. This study aimed to evaluate the cardiovascular risk according to Framingham score in a cohort of HCV infected patients.
Methods. We conducted a cross sectional analysis on a cohort of 117 HCV infected patients compared to 30 controls. We recorded demographical data, HCV infection history, behavioral CV risk factors, personal and family history of CV events. We obtained fasting serum samples for lipid profile, glucid parameters, liver aminotransferases. Liver histology was assesed with Fibromax tests. CV risc was assesed with Framingham risk score. This is an interim analysis.
Results. Framingham risc score was similar in the two groups. Regarding behavioral CV risk factors, in HCV group significantly more patients declared low fat diet and higher fresh fruits and vegetables intake. Conversely, the HCV group reported lower physical activity levels. In bivariate analysis Framingham score was correlated to liver fibrosis, activity, steatosis and steatohepatitis scores (Spearman Coefficients 0.510, 0.365, 0.466 0.433, $p<0.001$ for all comparisons). However in logistic regression this associations were not statistically significant.
Conclusion. CV risk assesed by Framingham score was similar in HCV infected and uninfected patients, although it is possible that Framingham score underestimates CV risk in HCV infected patients.

Keywords: cardiovascular risk, Framingham risk score, chronic hepatitis, HCV

BACKGROUND

A large amount of literature data support the idea that hepatitis C virus (HCV) infection is closely related to the host lipid and glucid metabolism. Alterations of lipid and glucid homeostasy, such as insulin resistance, dyslipidemia, liver steatosis, and chronic inflammatory syndrome represent pathogenic pathways that accelerate the progression of liver disease in chronic hepatitis C (CHC) patients. Also these metabolic disturbancies are involved in atherogenesis progression and increase the risk of cardiovascular (CV) events.

The link between HCV infection and atherogenesis is supported by a number of epidemiological studies. Adinolfi et al (1) reported that CHC patients had a significantly higher prevalence of carotid atherosclerosis, in a study on 326 CHC patients and 477 uninfected. Similary, Boddi et al, (2) reported a higher prevalence of carotid atheromatosis in HCV-infected, in a study on 31 CHC patients and 120 controls.

A few years later the same team managed to prove a direct proatherogenic role of HCV. The authors (3) reported the presence of HCV genome in the foam core of carotid plaques in a study on 7

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HCV-seropositive patients with carotid revascularisation, of which 3 had undetectable HCV serum viral load.

Although some clasic CV risk factors are associated to HCV infection, literature data regarding the risc of CV events in HCV infected patients are conflicting. For example Butt et al (4) reported a 27% higher risc for coronary artery disease in CHC patients, in a large cohort study on over 82.000 HCV infected patients and over 90.000 controls. Similar results were reported by Kakinami et al, (5) who found a 2.4% higher CV risk evaluated with the Framingham score in CHC patients.

On the other hand, Arcari et al (6) found no significant correlation between the risk of miocardial infarction and HCV seropositivity in a cohort of 292 HCV infected compared 1:1 to uninfected subjects. Also Forde et al, (7) in a large cohort consisting of 48.000 HCV infected patients and over 70.000 controls reported a similar risk of miocardial infarction in infected and uninfected patients.

This conflicting results might be due to the fact that these studies evaluated populations with different characteristics in regard to the prevalence of various CV risk factors.

Our study aimed to asses the cardiovascular risk in chronic HCV infected patients in relation to disease progression and treatment response.

METHODS

We condicted a non-interventional cross sectional study on HCV infected patients monitored in a tertiary infectious diseases hospital in Bucharest, which presented for follow-up between December 2012- August 2013.

We included HCV infected adults who were able to sign an informed consent, also non-infected patients for the control group. We excluded patients with acute or chronic inflammatory diseases, chronic liver conditions HBV or HIV co-infected, and patients with diabetes mellitus.

We enrolled 147 patients, divided in 5 groups as follows:

- Previously treated HCV infected patients with sustained virological response, n=31;
- Previously treated HCV infected patients with virological failure, n=30;
- Untreated HCV infected patients with chronic hepatitis n=30;
- Untreated HCV infected patients with liver cirrhosis, n=26;
- Uninfected patients – the control group, n=30;

Ethical committee approval was obtained and all patients signed an informed consent.

We recorded demographic data, information on HCV infection history, personal and family history of cardiovascular events and risk factors, food habits, physical activity status, smoking. We measured height and weight for body mass index (BMI), waist and hips perimeter for waist to hip ratio (WHR), blood pressure.

Subsequently we obtained fasting blood samples for lipid profile, serum glucose, glycosylated hemoglobin, liver enzymes (ALT, AST). Liver histology was assessed with non-invasive tests Fibromax (Biopredictive, France). CV risk was estimated with Framingham risk score.

For statistical analysis we use SPSS software (California, USA), version 21.0. This is an interim analysis.

RESULTS

Patient characteristics

We enrolled a total of 117 patients and 30 controls between December 2012 and August 2013.

Patient characteristics are presented in table I. Although we intended to have a control group matched by sex and age, by enrolling in the control group the partners of the patients, in the end the control group had a significantly lower median age: 47 years versus 54, p=0.042. As it was expected, median serum values of AST, ALT, GGT and bilirubin were higher in HCV infected group.

The 10-years CV risk was similar between HCV infected patients and the control group. Lipid profile was similar in the two groups, with exception of serum cholesterol which had a significantly higher median value in control group.

Regarding behavioral CV risk factors (table II), a significantly higher percent in the infected group declared a low fat diet (44.8% versus 22.6%, p<0.001); also in the infected group a higher percent of patients declared daily consumption of fresh fruits and vegetables (75.9% versus 54.8%, p<0.001). The physical activity level was higher in the control group.

Regarding liver histology (figure 1), 37 patients (31.8%) had cirrhosis, 37 (31.8%) had a moderate fibrosis score (F2-3) and 30 (25.8%) had mild or no fibrosis (F0-1). Fourty seven patients (40.5%) had moderate and severe activity index (A2-3), 26 (22.4%) had moderate and severe steatosis (S2-3) and 14 patients (12.0%) had a moderate score of non-alcoholic steatohepatitis (Nash) (N2). The mean viral load was 5.80 log UI/ml (IQR 5.26-6.33).

TABLE 1. *Patient characteristics*

	Patients N = 117	**Controls N = 30**	**p**
Age (years) – median [IQR]	54 [45-61]	47 [39-57]	0.042
Males – nr. (%)	41 (35%)	13 (42%)	NS
AST UI/ml – median [IQR]	44 [28-77]	25 [21-30]	0.000
ALT UI/ml – median [IQR]	65 [41-109]	33 [26-47]	0.000
GGT UI/ml – median [IQR]	34 [21-77]	23 [18-38]	0.050
Bilirubin mg/dl – median [IQR]	0.8 [0.7-1.0]	0.7 [0.5-0.9]	0.033
Albumin g/L – median [IQR]	4.37 [4.12-4.55]	4.46 [4.18-4.53]	NS
Framingham score – median [IQR]	2 [1-5.7]	3 [1-8]	NS
Cholesterol mg/dl – median [IQR]	179 [155-214]	213 [174-240]	0.007
LDL mg/dl – median [IQR]	102 [78-132]	137 [93-162]	NS
HDL mg/dl – median [IQR]	54 [41-64]	56 [46-63]	NS
Triglycerides mg/dl – median [IQR]	104 [75-148]	97.5 [57-144]	NS
Glucose mg/dl – median [IQR]	91 [86-99]	92 [87-101]	NS
Glycosylated hemoglobin % – median [IQR]	5.37 [5.06-5.56]	5.41 [5.22-5.55]	NS
BMI Kg/m^2 median [IQR]	25.3 [22.7-28.3]	26.2 [24.2-29.8]	NS
BMI > 25 Kg/m^2	64 (55.6%)	21 (70%)	NS
BMI > 30 Kg/m^2	19 (16.5%)	6 (20%)	NS
WTH > N*	96 (82.8%)	26 (83.9%)	NS

Legend: IQR = interquartile range; AST = aspartate aminotransferase; ALT = Alanine aminotransferase; GGT = gamma-glutaril transpeptidase; LDL = low density lipoproteins; HDL = high density lipoproteins; BMI = body mass index; WTH = waist to hip ratio; NS = not significant.
*Normal waist to hip ratio was considered < 0.7 in females and < 0.9 in males

TABLE 2. *Behavioral and family cardiovascular risk factors*

	Patients N = 116	**Controls N = 30**	**p**
Smokers	35 (30.4%)	13 (41.9%)	NS
Personal history of CV risk factors			
None	73 (58.1%)	18 (58.1%)	NS
High blood pressure	26 (22.4%)	5 (16.1 %)	NS
Dyslipidemia	9 (7.8%)	6 (19.4%)	NS
CAD/Stroke	3 (2.6%)	0 (0%)	NS
Number of family members with CV disease			
0	82 (70.7%)	19 (61.3%)	0.000
1	25 (21.6%)	12 (38.7%)	0.033
2	8 (6.9%)	0 (0%)	-
Diet			
None	39 (33.6%)	19 (61.3%)	0.009
Low lipids	52 (44.8%)	7 (22.6%)	0.000
Low calories	3 (2.6%)	2 (6.5%)	NS
Low sodium	3 (2.6%)	0 (0%)	NS
Animal fat excess	3 (2.6%)	2 (6.5%)	NS
Meat consumption			
Pork	9 (7.8%)	9 (29.0%)	NS
Beef	15 (12.9%)	2 (6.5%)	0.002
Chicken	80 (69.0%)	8 (58.1%)	NS
Fish	11 (9.5%)	2 (6.5%)	NS
Fruit/vegetable consumption			
Daily	88 (75.9%)	17 (54.8%)	0.000
> 3 x/week	8 (6.9%)	8 (25.8%)	NS
< 3 x/week	19 (16.4%)	6 (19.4%)	0.009
Physical activity*			
> 4 h/week	57 (49.1)	23 (74.2)	0.000
2-4 h/week	29 (25.0)	6 (19.4)	0.000
< 2 h/week	29 (25.0)	2 (6.5)	0.000

Legend: CV = cardiovascular; CAD = coronary artery disease
*Mild physical activity

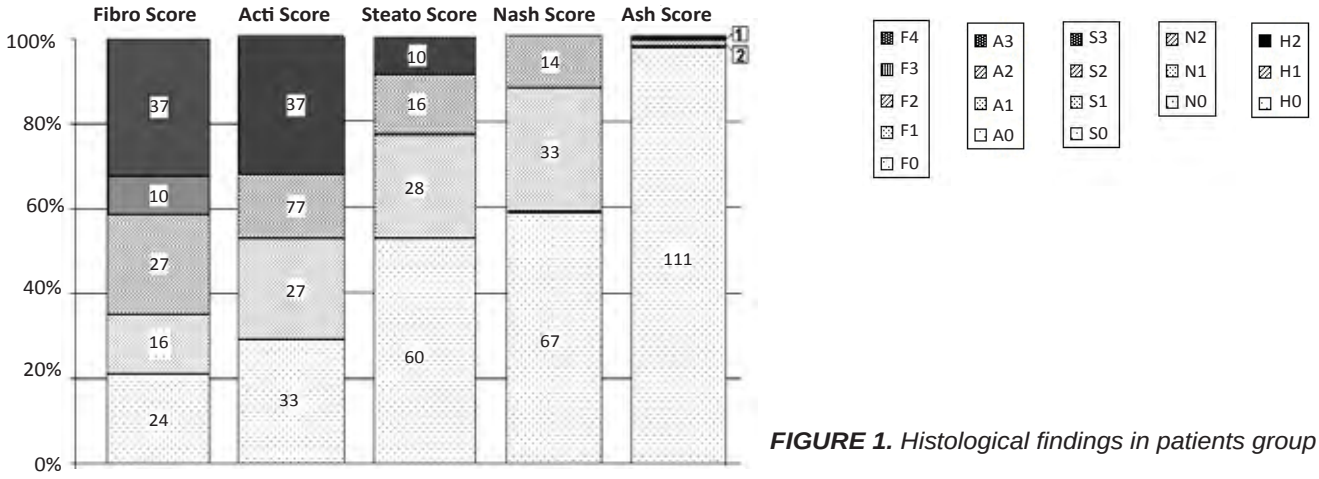

FIGURE 1. *Histological findings in patients group*

In bivariate analysis CV risk was significantly correlated to fibrosis, liver inflammatory activity, steatosis and Nash (figure 2) with Spearman coefficients of 0.510, 0.365, 0.466 and 0.433, p<0.001 fo all comparisons. However in logistic regression, after adjusting for sex and age these correlations did not remain statistically significant.

Framingham score was similar between patients with virological response to previous treatment and those with virological failure.

DISCUSSIONS

In our study, the 10-years CV risk assesed by Framingham risk score was similar in HCV-infect-

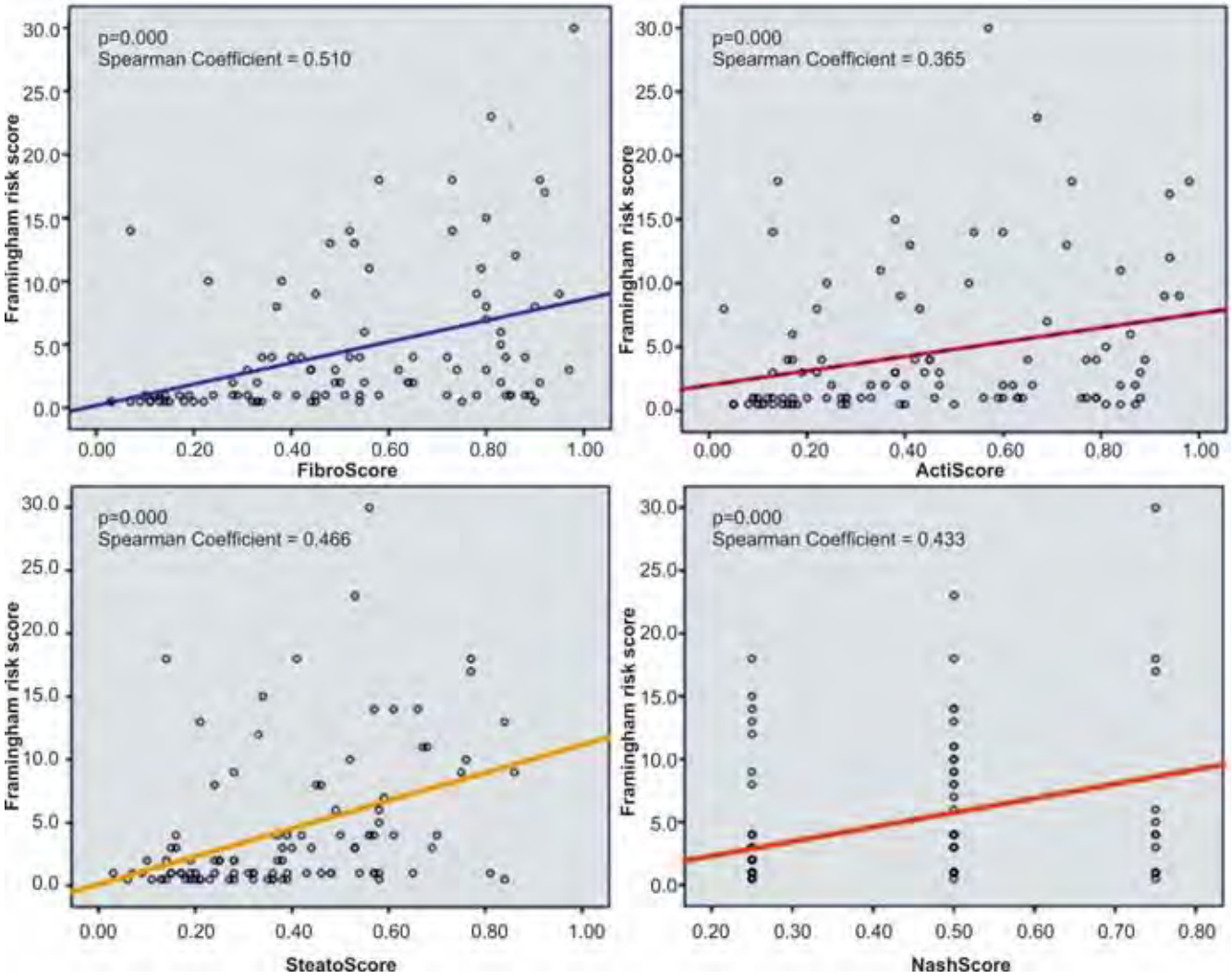

FIGURE 2. *Correlation charts between Framingham risk score and liver histology scores*

ed and control group. A posible limitation to our findings is the fact that the uninfected subjects were younger.

However, considering that the infected group included cirrhotic patients, it would be expected – at least in these patients – that liver glucogenesys and lypogenesys were reduced. Lower serum lipids and glucose imply a better Framingham score. On the other hand, some metabolic disturbancies related to chronic HCV infection, such as insulin-resistance, chronic inflammation, obesity, liver steatosis should lead to an increased CV risk. Literature data are inconsistent in this matter. Some authors reported a higher CV risk in CHC patients, (4, 5) while others found no difference between HCV- infected and uninfected patients. (7)

In our study, although in bivariate analysis Framingham score was significantly correlated to all liver histology scores, in logistic regression, after adjusting for sex and age this correlations lost their statistical significance. However, a link between CV risk and liver fibrosis is conceivable, if we consider that the factors that concur to atheromatous plaques progression in coronary or cerebral arteries can have the same consequence in liver arteries, with chronic hipoxia of the liver, which could accelerate fibrogenesis. Moreover, metabolic disturbancies associated to chronic HCV infection, such as insulin-resistance for example, are themselves involved in atherogenetic process and increase of cardiovascular risk. Thus, a patient with advanced fibrosis – which means a longer length of infection, or a patient with high liver inflammation – with a very active disease – should have an acceleration of atherogenesis, and a higher CV risk.

On the other hand cirrhotic patients tend to have lower blood pressure – which is an important criteria in the Framingham risk score. Multiple mechanisms concure to lower blood pressure in patients with advanced fibrosis: reduced liver metabolisation of vasodilatators, such as nitric oxide, periferic resistance to vasopressors and an increased distribution of blood volume in the portosystemic collateral vessels. (8)

Considering the ideas discussed above, it's probable that Framingham score is not appropriate for evaluating the CV risk in HCV infected patients, as it disregards the lipid profile particularities and the tendency of periferic insulin-resistance and lower blood pressure in these patients. Hence, another CV risk estimator would be required for chronic HCV infected patients. A good option for a criteria in such a risk score adapted to CHC patients would be liver steatosis or steatohepatitis, since non-alcoholic steatohepatitis is now considered the liver expression of metabolic syndrome and an independent CV risk factor. (9)

CONCLUSIONS

Cardiovascular risk was similar in HCV infected and uninfected patients, although Framingham risk score might not be the best tool to evaluate CV risk in CHC patients.

A large amount of literature data proved a close link between chronic HCV infection and the host's glucid and lipid homeostasy, with important impact on liver disease progression and an incresed risk of CV events and diabetes mellitus. Although important progress has been made in the last decade in understanding the fine pathophysiological processes involved in chronic HCV infection, many aspects remain unclear. However it is certain that chronic hepatitis C can no longer be regarded as a simple liver disease, but as a complex condition, with systemic consequences.

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