Differences Between Risk Factors and Impact on Antiviral Therapy of Insulin Resistance in Chronic Hepatitis B and C Patients

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Background: Hepatitis C virus infection seems to induce insulin resistance and type 2 diabetes by direct viral involvement. The prevalence of glucose metabolism disorders is higher in C virus infected non-cirrhotic patients in comparation with patients with other etiology liver diseases.
Material and method: Two-hundred seventy patients with chronic C hepatitis were compared to 163 patients with chronic B hepatitis, regarding glucose metabolism before and after antiviral therapy and regarding the risk factors of diabetes.
Results: The prevalence of insulin resistance was 19% in hepatitis C and 6.7% in hepatitis B patients ($p<0.0001$). 90.2% of insulin resistant patients with C hepatitis had viraemia ≥800,000UI/ml. After viral eradication plasma glucose and insulin levels decreased significantly ($p<0.0001$). In this group of patients, eradication was obtained less (66.7%) than in the non-insulin resistent C hepatitis (84.4%) or insulin resistant B hepatitis group (80.0%).
Conclusions: Hepatitis C virus infection increases the risk of diabetes compared with hepatitis B virus, irrespectively of classic diabetes risk factors, but dependent on viraemia. Insulin resistance decreases therapeutic response only in hepatitis C, but viral eradication improves glucose metabolism in these patients.

Keywords: hepatitis C, hepatitis B, insulin resistance

Received: 15 June 2012 / Accepted: 27 September 2012

Introduction

Chronic hepatitis C virus (HCV) infection has a considerable prevalence, with more than 200 milion persons infected worldwide. Eighty per cent of these are chronic infections and 60–70% are asymptomatic, presenting the risk of the development of cirrhosis or hepatic cancer.

The disease is important not only because of the involvement of the liver, but also because of the extrahepatic complications, which can influence the response to treatment and can affect the prognosis [1,2,3].

Type 2 diabetes is the 5th cause of mortality worldwide, with almost 3 million deaths yearly. More than 3% of the world's population is affected, but the number of latent cases is even higher. Chronic complications and the associated cardiovascular diseases represent the major problem linked to diabetes. Most of the diabetic patients are middle aged (45–64 years old), being part of the active population. This fact increases the economic impact of the disease. Data from the World Health Organisation show that the number of cases will be double in 2030 and mortality caused by diabetes will increase by 50% in the next 10 years, without interventions. Five per cent of the Romanian population is affected by glucide metabolism disorders [4].

One of the most important extrahepatic complications of chronic hepatitis C, and also one of its aggravating factors is insulin resistance or type 2 diabetes [5,6]. They can appear independently of the hepatic disease, but epidemiologic studies have demonstrated the increased prevalence of insulin resistance in HCV infected persons without cirrosis. This phenomenon may not be observed in case of other chronic hepathopathies, like hepatitis B, autoimmune or alcoholic hepatitis. Experimental data suggest that HCV influences glucose metabolim directly and indirectly, but the patomechanisms are not ellucidated yet [7,8].

The association of chronic C hepatitis and diabetes is important not only because insulin resistance accelerates the evolution of hepatitis, but it is also able to decrease therapeutic response [9].

The aim of this study was to identify the risk factors of insulin resistance and diabetes in patients infected with hepatitis C virus compared with patients infected with hepatitis B virus, the effects of metabolic disorders on therapeutic response and the effects of viral eradication on glucose metabolism.

Material and method

Four-hundred thirty-three patients (17–65 years old) with chronic viral hepatitis were included in the study, they underwent liver biopsy in the Clinic of Gastroenterology of the University of Medicine and Pharmacy Târgu Mureş and the Department of Gastroenterology of the Odorheiu Secuiesc Municipal Hospital between January 2007 and December 2010. Patients with cirrhosis, history of diabetes, pancreatic or autoimmune diseases and cancer were excluded. We also excluded patients who had chronic steroidic or other therapy that can influence glucose metabolism.

We determined the type of infection (HBs antigen, anti-HCV antibody) by ELISA method and the viral load by polymerase chain reaction. The study group included

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HCV infected patients, while the control group included HBV infected patients.

After measuring the initial glucose metabolism parameters, we created 4 groups of patients:

A. Hepatitis B with normal glucose metabolism;
B. Hepatitis B with insulin resistance/diabetes;
C. Hepatitis C with normal glucose metabolism;
D. Hepatitis C with insulin resistance/diabetes.

All subjects have been evaluated regarding diabetes risk factors such as age, family history of diabetes, personal history of cardiovascular disease, hyperlipemia, glucose abnormalities, gestational diabetes, macrosomia, obesity (body mass index, type of obesity).

We determined serum glucose, serum insulin a jeun and after oral loading with 75 g glucose. We calculated insulin resistance by homeostasis model assessement (HOMA-IR): HOMA-IR = a jeun serum glucose level (mg/dl) x a jeun serum insulin level (μUI/ml) / 405 before and after antiviral therapy. We also followed the success of viral eradicaton after therapy, correlated with patients' metabolic status.

Statistical analysis was performed using Microsoft Excel and SPSS 15 programs. We used descriptive and interferencial statistical methods and Chi^2, Mann-Whitney and Kruskal Wallis tests.

Results

We have followed 433 patients: 163 infected with HBV and 270 infected with HCV. We made clinical and paraclinical evaluation and perforemd liver biopsies.

Following antiviral therapy we were able to measure glucose metabolism parameters in 41.7% of the HBV infected patients and 48.7% of the HCV infected patients, given that some of them could not receive antiviral treatment, others have not finished it until the end of our study and a small number of patients did not come back after they finished the therapy.

After the first measurements of a jeun and 2-hour (after oral load) blood glucose level, insulin level and HOMA value, we observed a statistically significant difference ($p<0.0001$) between HBV (6.7%) and HCV (19%) patients regarding the presence of glucose metabolism disorders (insulin resistance or diabetes).

There was a significant difference ($p<0.0001$) between the mean age of HBV (42.41 years) and HCV (47.64 years) patients. The mean age of the 4 groups: group A: 41.80 years, group B: 50.91 years, group C: 47.32 years, group D: 49.04 years. The difference was significant between group A and B ($p=0.027$), but not between groups C and D. Nevertheless the HCV patients group was older, insulin resistance appeared in younger patients than in the HBV group.

Android obesity, which increases the risk of diabetes, was more frequent in HCV patients (48.3%) than in HBV patients (31.9%), with a statistically significant difference ($p<0.0001$). Abdominal adiposity appeared in 27% of group A patients, 100% of group B, 47.7% of group C and 51.0% of group D patients. We found a significant difference only between groups A and B ($p<0.0001$), but not between groups C and D.

Mean body mass index was 24.55 in HCV patients (normal) and 26.19 in HBV patients (overweight). The difference was statistically significant ($p<0.0001$) between groups A (25.77) and B (32.07), but not between groups C (24.81) and D (23.44) ($p=0.840$).

Family history of diabetes was present in 8.6% of HBV patients and in 3.3% of HCV patients ($p=0.19$). In our groups, this risk factor showed the following distribution: group A: 2.6%, group B: 90.9%, group C: 3.2%, group D: 3.9%.

Arterial hypertension appeared in 15.3% of HBV patients and in 19% of HCV patients, without significant difference ($p=0.338$). Hypertension was present mostly in group B, with the following results in the 4 groups: A: 11.8%, B: 63.6%, C: 21.1%, D: 9.8%.

Gestational diabetes and macrosomia were present in 1.8% of the HBV group and in 2.6% of the HCV group ($p=0.610$). There was a significant difference between groups A (0.7%) and B (18.2%) ($p<0.0001$), but not between groups C and D ($p=0.749$).

HBV positive insulin resistant patients had generally cumulated 2 or more diabetes risk factors. The patients of the other groups had no risk factors in most cases. The number of classic diabetes risk factors of each group is presented in Figures 1–4.

17.8% of the hepatitis B patients and 4.5% of the hepatitis C patients had hypercholesterolemia ($p<0.0001$). Comparing the groups, there was a significant difference between diabetic and non-diabetic individuals in both the HBV ($p<0.0001$) and the HCV ($p=0.005$) group. Mean serum cholesterol was normal in both HBV (168.12 mg/dl) and HCV (151.57 mg/dl) groups. The 4 groups had the following mean cholesterol levels: A: 162.32 mg/dl, B: 248.36 mg/dl, C: 147.17 mg/dl, D: 170.33 mg/dl. The difference between the insulin resistant groups (B and D) was statistically significant ($p<0.0001$).

8.6% of HBV and 3.3% of HCV patients had hypertriglyceridemia ($p<0.0001$). Group analysis showed a significant difference between A–B ($p<0.0001$) and also C–D ($p=0.005$) groups. The mean triglycerid level was 118.69 mg/dl in HBV infected patients, and 111.38 mg/dl in HCV infected patients. The 4 groups had the following mean triglycerid levels: A: 114.44 mg/dl, B: 177.36 mg/dl, C: 111.01 mg/dl, D: 112.71 mg/dl. The difference was significant only between groups A and B ($p<0.0001$).

Mean fasting plasma glucose of HBV patients (93.21 mg/dl) differed significantly from HCV patients' glucose level (1í2.94 mg/dl) ($p<0.0001$). A significant difference ($p<0.0001$) also appeared between groups A (91.4 mg/dl) and B (118.27 mg/dl), and C (98.83 mg/dl) and D (120.49 mg/dl) respectively.

Mean plasma glucose after oral load showed significant differences ($p<0.0001$) between HBV (114.37mg/dl) and HCV (134.73 mg/dl) patients, but also between groups A

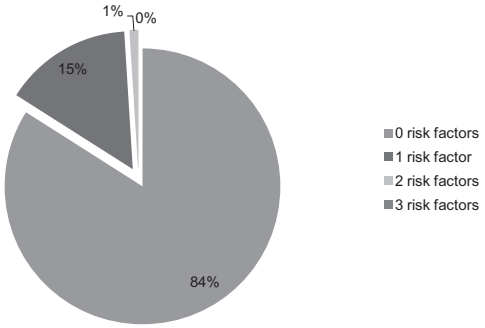

Fig. 1. Distribution of the number of diabetes risk factors in group A

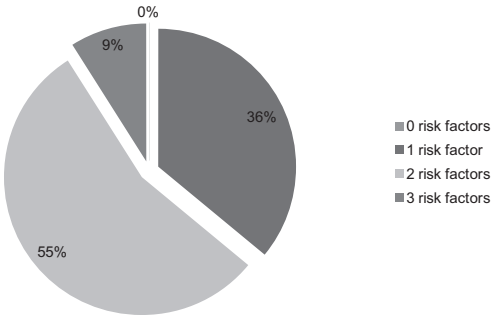

Fig. 2. Distribution of the number of diabetes risk factors in group B

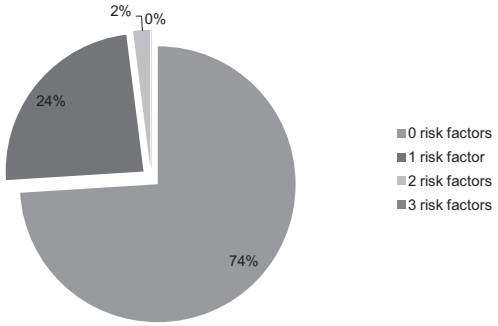

Fig. 3. Distribution of the number of diabetes risk factors in group C

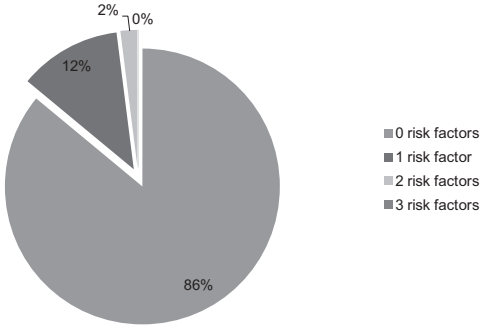

Fig. 4. Distribution of the number of diabetes risk factors in group D

(110.2 mg/dl) and B (172.09 mg/dl), and C (124.33 mg/dl) and D (179.18 mg/dl) respectively.

Mean fasting insulin level of HBV patients (8.72 μUI/ml) differed significantly from HCV patients' insulinaemia (10.36 μUI/ml) ($p<0.0001$). The difference was also significant ($p<0.0001$) between groups A (7.99 μUI/ml) and B (18.91 μUI/ml), and C (8.27 μUI/ml) and D (19.33 μUI/ml) respectively.

Mean HOMA value was 1.127 in the HBV and 1.401 in the HCV group ($p<0.0001$). Group analysis showed the following values: A: 1.02, B: 2.57, C: 1.10, D: 2.63 ($p<0.0001$ between groups A–B and C–D respectively).

45.4% of HBV infected patients had low viral load (less than 800,000UI/ml), 54.6% had high viral load (more than 800,000UI/ml); 34.6% of HCV infected patients had low viral load, 65.4% high viral load. The results by groups are the following: group A – 44.7% low viral load 55.7% high viral load; group B – 54.5% low viral load, 45.5% high viral load; group C – 40.4% low viral load, 59.6% high viral load; group D – 9.8% low viral load, 90, 2% high viral load. The difference was statistically significant between groups C and D ($p<0.0001$), but not between groups A and B ($p=0.528$).

After antiviral therapy, fasting plasma glucose was 96.83 mg/dl in HBV and 103.18 mg/dl in HCV infected patients. We did not observe significant differences between glycaemia before and after treatment within one cohort. Posttherapeutic fasting glycaemia of our groups of patients: group A: 93.19 mg/dl, group B: 115.36 mg/dl, group C: 100.2 mg/dl, group D: 109.95 mg/dl. Fasting glucose decreased significantly after viral eradication only in group D ($p<0.0001$) (Figure 5).

Posttherapeutic mean plasma glucose after oral load showed the following values: HBV: 120.63 mg/dl, HCV: 133.66 mg/dl; group A: 110.96 mg/dl, group B: 170.73 mg/dl, group C: 124.38 mg/dl, group D: 154.05 mg/dl.

Plasma insulin levels after therapy: HBV: 9.52 μUI/ml, HCV: 10.57 μUI/ml; gruop A: 7.95 μUI/ml; group B: 18.50 μUI/ml; group C: 8.13 μUI/ml; group D: 16.69 μUI/ml.

Posttherapeutic HOMA-IR increased (but not significantly) in both HBV (1.222) and HCV (1.665) groups. Group HOMA values after treatment: A: 1.02, B: 2.38, C: 1.44, D: 2.24. All these parameters decreased significantly after viral eradication only in group D ($p<0.0001$).

We obtained virus eradication in 75.6% of HBV and in 78.6% of HCV infected patients, without significant difference between them regarding therapeutic success ($p=0.282$). Responder patients in the 4 groups: A: 74.0%, B: 80.0%, C: 84.4%, D: 66.7%. There was a significant difference between groups C and D ($p=0.012$), but not between groups A and B ($p=0.282$).

Discussions

Since most literature data affirm that older age, higher body mass index, elevated serum lipids, family history of diabetes and personal history of hypertension, gestational diabetes or macrosomia have no influence on the glucose metabolism of HCV infected patients [10,11], we followed these parameters in our cases.

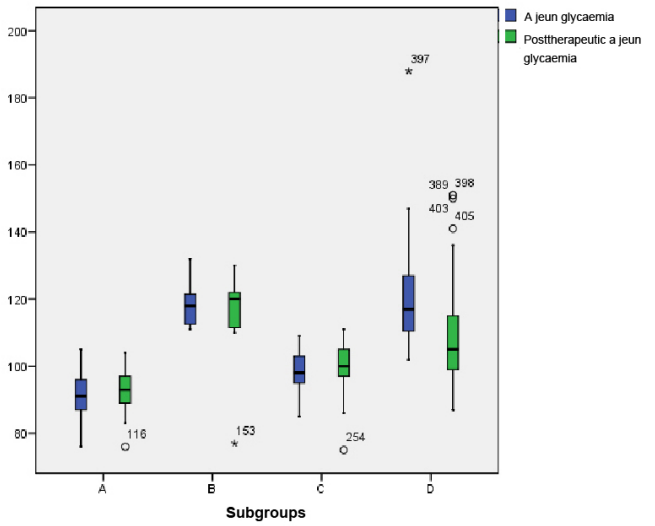

Fig. 5. Basal blood glucose level of patient groups before and after antiviral therapy

The HCV group was „older" with 5 years than the HBV group, but group analysis showed that older age correlates with insulin resistance only in HBV infected patients. It is known that the incidence of type 2 diabetes increases with age in the general population [4], a tendency observed in our HBV (but not HCV) patients. Moreover, the insulin resistant HCV group (D) had a lower mean age than the non-insulin resistznt HCV group (C). Other studies have come to the same conclusion: diabetes in HCV positive individuals appears at younger age than in control subjects [10].

Android obesity appeared in all patients of group B and in a small proportion in group A. On the other hand, there was no difference regarding the type of obesity between HCV positive groups.

Mean body mass index of HBV infected patients was over 25 (overweight), but HCV patients had the mean value in normal range. Group B stepped over the obesity limit, but, interestingly, group D was „leaner" than group C (without significant difference). It seems that obesity is associated with diabetes in case of B hepatitis, but not C hepatitis.

Family history of diabetes, arterial hypertension, gestational diabetes and fetal macrosomia appeared in the majority of group B patients, but these risk factors were present in low and approximately equal proportions in all the other groups.

Literature data regarding the role of classic diabetes risk factors in HCV-linked insulin resistance are controversial. Some researchers found that family history is associated with diabetes in HCV positive patients, but anthropometric data have no influence [10,12,13]. Others found a link between android obesity, age and diabetes in these patients [14,15]. There are some studies that observed a lower body mass index and younger age in HCV infected diabetic patients compared with non-infected diabetic patients [10].

Anyway, our results showed that classic diabetes risk factors are important in B-, but not in C-hepatitis linked diabetes.

Mean plasma lipid levels (cholesterol, triglycerides) were in normal range in groups A, C and D, being elevated only in group B. Hypercholesterolaemia and hypertriglyceridaemia were significantly more frequent in both insulin resistant groups, but their prevalence was much higher in group B compared with group D. Consequently, hyperlipaemia is linked slightly to insulin resistance in VHC infected patients, but this association is more relevant in HBV infected patients. After all, our study showed some association between insulin resistance and dislipidaemia, contrary to other studies, which did not find any relationship [16].

High viral load (≥800,000 UI/ml) was present in more than half of patients independently of type of infection. In HBV infected patients high viral load appeared more often in the insulin resistant group (B: 54%), but the difference was much higher in HCV infected patients: 90% in the insulin resistant (D) and 60% in the normal metabolism (C) group. These data suggest that patients with HCV infection and higher viral load are predisposed to be insulin resistant. In HBV infected patients there is no relationship between viraemia and glucose metabolism. These findings were also described by other researchers too [12,17,18].

Before antiviral treatment the serum insulin level, fasting and 2 hours postprandial plasma glucose were significantly higher in patients with C hepatitis compared with B hepatitis patients. Mean glucose and insulin levels were in normal range in both cohorts. Mean HOMA-IR (insulin resistance indicator) was between 1–2 in both cohorts, but it was very close to 1 in HBV patients and close to 1.5 in HCV patients. Normal HOMA value is 1, if it is higher than 2 there is a clear insulin resistance. Between 1 and 2 (as we found in our HCV cohort), other data linked to glucose metabolism have to be analysed, because there could be an incipient insulin resistance.

Groups A and C had a mean HOMA value close to 1, B and D groups above 2, as it was expected.

Taking together HOMA values, plasma glucose and insulin levels, we found that 19% of the HCV infected patients had insulin resistance or diabetes. The same disturbances were present in just 6.7% of HBV infected patients. This last value is very close to the prevalence of diabetes in general population [4]. Therefore, the relative risk for glucose metabolism disorders of HCV patients compared with HBV patients is 2.83.

Literature data shows that hepatitis C virus infection increases insulin resistance and diabetes risk 2–4 times in comparison with healthy subjects or other hepatic disease [13,15,19,20,21], even after liver transplant [22,23], but there is no significant difference in diabetes prevalence between HCV infected or other etiology cirrhotic patients [24,25,26]. One study found a higher prevalence of diabetes even in C viral cirrhosis comparing to B viral cirrhosis

[27]. Anyway, plasma glucose, insulin and HOMA values are higher in C virus infected patients than in persons with other hepatic diseases with or without cirrhosis [5,16,26].

There are few researchers who did not find differences in glucose metabolism in B and C virus infected patients without obesity, steatosis, alcool consumption and normal liver enzymes. This finding suggests that steatosis, inflammation and fibrosis could play a role in the development of diabetes in HCV positive patients [28].

Considering our and other researchers' findings, it seems that HCV infection really increases the risk of type 2 diabetes, in spite of existing contradictions.

After antiviral therapy, virus eradication was obtained in more than 70% of patients. There was no statistically significant difference in therapeutic success between groups A and B, but the results of groups C and D differed significantly. Most patients with hepatitis C and normal glucose metabolism were responders and most of HCV infected insulin resistant patients were non-responders. These results conclude with most international findigs. Several studies found that glucose metabolism disorders decrease therapeutic response in HCV infected patients [8,29,30,31], so the improvement of insulin resistance could facilitate virus eradication [32,33,34,35]. There are some studies which could not obtain improvement of therapeutic success with insulin sensitising drugs [9,36], so there are contradictions in recent data. Anyway, lifestyle changes (diet, exercise) seems to improve insulin sensitivity and the evolution of hepatic disease in patients with chronic C hepatitis, but they are inefficient in those with chronic B hepatitis. Therefore these methods should be adopted by all patients infected with HCV [9,27,36,37,38].

Posttherapeutic evaluation of our patients showed a significant reduction of plasma glucose, insulin and HOMA values in group D, compared to initial values. Other groups (A, B, C) did not show any significant changes in glucose metabolism parameters. Similarily, most of researchers observed improvement of glicemia, insulinaemia and HOMA-IR after viral eradication [10,39,40,41] and there is a study that did not come to the same conclusion [14].

Conclusions

1. The prevalence of glucose metabolism disorders is almost 3 times higher in patients infected with HCV compared to patients infected with HBV.
2. Insulin resistance/diabetes in patients with chronic C hepatitis is different from insulin resistance/diabetes of chronic B hepatitis patients. The latter (excepting cirrhotic patients) shows the same characteristics as common diabetes. These data suggest that HCV probably affects glucose metabolism directly.
3. Metabolic disorders occure in younger patients in the presence of HCV infection, than in the presence of HBV.
4. Android obesity increases the risk of diabetes only in HBV infected patients, but not in those infected with HCV.
5. Classic diabetes risk factors as family history of diabetes, arterial hipertension, personal history of gestational diabetes or macrosomia have no significant influence on diabetes in HCV cases, but they increase the risk of diabetes in HBV cases.
6. Elevated serum lipid levels have a minimal impact on insulin resistance linked to hepatitis C, but they are important risk factors in case of hepatitis B.
7. Even in HCV infected patients without insulin resistance glucose metabolism parameters (glicaemia, insulinaemia and HOMA) are somewhat higher compared with HBV infected patients. This fact can suggest a disposition for diabetes.
8. High viral load is an important risk factor of diabetes only in HCV infected patients.
9. Both insulin resistance and diabetes decrease therapeutic response in chronic hepatitis C patients, therefore screening, prevention and treatment of glucose metabolism disorders are important.
10. Virus eradication improves glucose metabolism in C hepatitis, but it has no metabolic effect in B hepatitis. That is why antiviral therapy has to be started soon after diagnosis, even with patients without liver fibrosis, if insulin resistance and HCV are present.
11. Taking into account the results of our study, we consider the screening and prevention of insulin resistance and diabetes very important for all patients infected with HCV, without reference to the stage of disease.

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