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METABOLIC FACE OF CHRONIC HEPATITIS B AND C IN BULGARIA

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SUMMARY

It is well known that NAFLD, as well as diabetes mellitus (DM), correlated with the progression of liver fibrosis in chronic hepatitis C (CHC). The impact of NAFLD overlap in chronic hepatitis B (CHB) is not well established.

Aim. In this study we compared the prevalence of NAFLD and related metabolic parameters in CHC and CHB, and their relationship with disease activity and fibrosis.

Methods. The parameters of metabolic syndrome (MetS), glucose, insulin, HOMA-IR and histological features of steatosis / steatohepatitis were investigated in total of 700 patients with chronic viral hepatitis - CHB (n=334) and genotype 1 CHC (n=366). Glucose and insulin were also assessed during OGTT (60 and 120 min.) in 100 cases with CHB and 100 – with CHC.

Results. Nonalcoholic metabolic related steatosis was more frequent (62% v/s 48%) and severe in CHC compared to CHB ($p<0.01$). MetS (51% v/s 33%), and DM ^{OGTT} (30% v/s 20%) were found also in higher frequency in CHC than in cases with CHB ($p<0.001$). In the both type hepatitis insulin resistance was associated with disease activity. In CHC, but not in CHB, a positive correlation between the degree of steatosis and the activity score was found ($r = 0.322$, $p<0.05$). In 70% of the cases with CHB and severe steatosis (>66%) HBV DNA was negative or <10 000 copies/ml. The advanced liver fibrosis (F3-F4) was associated with moderate or severe steatosis (CHC), as well as with the glucose levels, markers of insulin resistance, and presence of DM ($p<0.001$), but not with the other components of metabolic syndrome.

In conclusion, nonalcoholic metabolic related steatosis, diabetes mellitus and insulin resistance are associated with the both viral hepatitis, but the prevalence is higher in chronic hepatitis C. The degree of steatosis correlates with the activity grade and stage of fibrosis only in patients with chronic hepatitis C. Insulin resistance and diabetes mellitus are associated with more advanced liver fibrosis in the both viral hepatitis.

Key words: hepatic steatosis, metabolic syndrome, insulin resistance, diabetes mellitus, chronic hepatitis C, chronic hepatitis B

It is well established that liver steatosis, insulin resistance, and diabetes mellitus have a synergic effect to accelerate the progression of liver damage in chronic hepatitis C genotype 1 (CHC) to cirrhosis and hepatocellular carcinoma (1, 2, 3). In addition metabolic but not viral-induced steatosis as well as obesity, insulin resistance and diabetes mellitus are factors of resistance to antiviral treatment. On the other hand the impact of nonalcoholic fatty liver disease (NAFLD) overlap in chronic hepatitis B (CHB) is not well established yet (4).

In this study we evaluated and compared the prevalence of NAFLD and related metabolic parameters in CHC and CHB, and their relationship with disease activity and fibrosis.

MATERIALS AND METHODS

A total of 700 patients with chronic viral hepatitis were included in this retrospective and prospective study (tabl. 1). The patients were divided in two groups. Group I included 334 cases with CHB and group II – 366 cases with CHC genotype 1.

The diagnosis of chronic hepatitis B and C, as well as diabetes mellitus was based on the standard criteria. Histological grading and staging of chronic viral hepatitis was assessed by METAVIR scoring system, and for evaluation of the steatosis and steatohepatitis we used Brunt's criteria (5). The patients with severe liver dysfunction, and alcohol consumption more than 20g/daily for women and 40g per day for men, and significant comorbidity which could interfere the study results were excluded.

For the diagnosis of metabolic syndrome we used NCEP, ATP III criteria11. Blood glucose and insulin levels were investigated in fasting stage, and HOMA – IR was calculated in all cases. In addition, these parameters were also evaluated on the baseline, 60^{th} and 120^{th} min of the standard oral glucose tolerance test (OGTT) with 75g glucose in 200 of the patients (100 with CHB and 100 with CHC). The criteria for insulin resistance included HOMA – IR >2.5, and/or insulinaemia > 100 UI/ml of the OGTT (6, 7).

Statistical methods included Mann-Whitney test, Anova, nonparametric and parametric correlation analysis.

RESULTS

Liver steatosis was observed in 160 of the patients with CHB (48%) and in 227 cases with CHC (62%). The portions of mild (5-33%), moderate (33-66%) and severe degree (> 66%) of steatosis were 49%, 24% and 27% for CHB, and 20%, 56% and 24% for CHC respectively. Nonalcoholic steatosis was more frequent and severe in patients with CHC compared to CHB ($p<0.01$). In addition steatohepatitis was observed in liver specimens in 15% (n=24) and 18% (n=41) for patients with CHB and CHC respectively.

Metabolic syndrome was found in 110 (33%) and 185 (50.5%) patients with CHB and CHC respectively. The percentage becomes even higher - 45.8% (n=153) for CHB and 55.1% (n=202) for CHC, when we included cases with presence of 2 components of metabolic syndrome. Two or more components of metabolic syndrome were presented mostly in patients with steatosis, in 95.6% (153/160) and 88.9% (202/227) for patients with CHB and CHC respectively ($p<0.001$). The metabolic parameters in patients with chronic viral hepatitis and steatosis are presented in table 2, and the impairment of glucose levels (fasting and during OGTT), among all of the patients and those with or without steatosis, are shown in table 3 and 4. Impaired fasting glucose and glucose tolerance, as well as diabetes mellitus were presented mostly in patients with steatosis, as well as in those patients with CHC ($\chi 2 = 86.4$, $p<0.001$). The mean levels of the fasting insulin and those on OGTT, as well as HOMA – IR, were higher in patients with steatosis compared to those without steatosis, especially in cases with CHC ($p=0.001$).

We found a positive relationships between the presence of steatosis and the age of the patients ($\chi 2 = 93.4$, $p<0.01$); the metabolic syndrome and its components ($\chi 2 = 123.6$- 158.7, $P<0.001$, and $r = 0.547$- 0.644, $p<0.001$); the blood glucose levels ($r = 0.747$, $P<0.001$) and presence of diabetes mellitus ($\chi 2 = 163.9$, $P<0.001$); the fasting insulin levels ($r = 0.530$, $P<0.001$) and HOMA – IR ($r = 0.684$, $P<0.001$), as well as GGT levels ($r = 0.560$, $P<0.001$) for both viral hepatitis. In CHC, but not in CHB, there were positive correlations between the presence of steatosis ($r=0.322$, $p<0.05$), as well as severity of steatosis or steatohepatitis ($\chi 2 = 85.5$, $P<0.01$, $r=0.347$, $p<0.05$), and activity grade or fibrosis staging.

No direct relationships between viral load and steatosis, as well as metabolic parameters as signs of metabolic syndrome, glycaemia and insulinaemia in both hepatitis were found. In 30 of 43 patients (70%) with CHB, and grade 3 steatosis (>66%) and/or steatohepatitis, HBV DNA was negative or less than 10 000 copies/ml.

In the both type hepatitis the hyperinsulinaemia was associated with disease activity ($r=0.432$, $p<0.01$). The glucose levels during OGTT ($r =0.399$, $p<0.01$), and/or the presence of diabetes mellitus ($\chi 2 = 134.2$, ($p<0.001$), as well as HOMA-IR ($r = 0.423$, $p<0.01$) and the degree of hyperinsulinaemia during OGTT ($r = 0.386$, $p<0.01$, $\chi 2 = 76.4$, $p<0.05$) also correlated with advance fibrosis (F3-F4).

DISCUSSION

Many data about relationship of CHC and steatosis, metabolic syndrome, obesity, insulin resistance as well as diabetes mellitus have been collected (1, 2, 3, 4). On the opposed only a small number of studies reported steatosis, obesity and MS prevalence in CHB have been published (4, 8, 9, 10). Some of them compared CHC and CHB for the prevalence of those metabolic factors. In our study we also evaluated and compared the prevalence of NAFLD and related metabolic parameters in CHC and CHB, and their relationship with disease activity and fibrosis.

The prevalence of steatosis of 62% in Bulgarian patients with chronic hepatitis C genotype 1 is near to the reported mean prevalence of 55%, with range of 38% to 80% (11, 12, 13). Our results also show a strong association between liver steatosis and metabolic syndrome. All metabolic disturbances were presented mostly in patients with steatosis. Like the results to the other authors, we also found the relationship between liver steatosis and hyperglycaemia and surrogate markers of insulin resistance, as well as disease activity and fibrosis staging. The prevalence of liver steatosis, insulin resistance and type 2 diabetes mellitus in patients with chronic hepatitis C is higher than reported in the general population (14). There is complex relationship between these factors. Every one of them is also an important independent co-factor in the worsening of liver disease (4, 15, 16). In addition these factors have a synergic effect to the progression of chronic hepatitis C to cirrhosis and hepatocellular carcinoma, and also can influence the response to antiviral treatment (16).

On the other hand, most of the data show that a steatosis prevalence in patients with CHB is similar to that of the general population (8, 9, 10, 17). In these studies the presence of steatosis correlates with BMI and metabolic parameters as waist circumference, high blood pressure and dyslipidemia, but not with viral genotype or viral load, and fibrosis (4, 8). We also found less prevalence and degree of steatosis as well as metabolic disturbances in CHB patients in Bulgaria than those with CHC. As HCV-related steatosis, steatosis in patients with CHB also associates with parameters of metabolic syndrome and markers of insulin resistance. In CHB patients with severe steatosis and/or steatohepatitis we observed low viral load or negative HBV DNA, but in generally there were no relationships between viral load and steatosis or metabolic parameters in both hepatitis.

On the opposite to CHC, steatosis in our patients with chronic HBV infection did not correlate with fibrosis. On the other hand hyperinsulinaemia as well as markers of insulin resistance were associated with disease activity and fibrosis in the both type hepatitis. Consecuently, in HBV related chronic hepatitis, steatosis is probably also a cofactor of liver disease worsening in patients with metabolic syndrome, diabetes mellitus or steatohepatitis.

CONCLUSIONS

Nonalcoholic metabolic related steatosis, diabetes mellitus and insulin resistance are associated with the both viral hepatitis, but the prevalence is higher in chronic hepatitis C.

The degree of steatosis correlates with the activity grade and stage of fibrosis only in patients with chronic hepatitis C.

Insulin resistance and diabetes mellitus are associated with more advanced liver fibrosis in the both viral hepatitis.

Table 1. Mean characteristic of the patients with CHB and CHC.

Markers	**Group I** (patients with CHB, n=334)	**Group II** (patients with CHC, n=334)
Average age (x±SD)	42.7±13.9	45.9±14.1
Sex – male/female (n)	122/112	165 / 201
ALAT (IU/L), (x±SD)	90.2±98.4	76.4±103.9
ASAT (IU/L), (x±SD)	64.4±72.0	52.0±48.2
GGT (IU/L), (x±SD)	46.3±52.2	55.2±49.4

Table 2. The metabolic parameters in patients with chronic viral hepatitis and steatosis.

Metabolic parameters	**CHB with steatosis** (n=160)	**CHC with steatosis** (n=227)
BMI (кg/ml), (x±SD)	25.9±3.5	25.5±3.3
Waist circumference (>102 cm /male >88 cm/female), (n/ %)	124 / 77.5%	181 / 79.7%
Hypertension (n / %)	51 / 31.8%	72 / 31.7%
Total cholesterol (mmol/l), (x±SD)	5.7 ±1.2	5.5±1.6
HDL- cholesterol (mmol/l), (x±SD)	0.95 ± 0.05	0.87 ± 0.08
LDL- cholesterol (mmol/l), (x±SD)	2.4 ± 0.2	2.6 ± 0.5
Triglycerides (mmol/l), (x±SD)	2.07± 0.4	2.3 ± 0.3
Fasting glucose (mmol/l), (x±SD)	4.8± 1.76	5.1±2.2

Table 3. The impairment of fasting glucose and insulin levels in patients with chronic hepatitis B and C, and those with or without steatosis.

Parameter	CHB			CHC		
	Total (n=334)	Steatosis (+), (n=160)	Steatosis (-), (n=174)	Total (n=366)	Steatosis (+), (n=227)	Steatosis (-), (n=139)
Impaired fasting glucose (6.1- 7.0 mmol/l), (%)	29/9%	24 /15%	5 /3%	42/12%	36 /16%	6 / 4%
Diabetes mellitus (fasting glucose >7.0 mmol/l), (n/%)	17/5 %	13/ 8%	4 / 2%	37 /10%	30 / 13%	7 / 5%
Fasting insulin (UI/ml), (x±SD)	17.9±6.4	20.4±10.2	13.2±4.2	18.4±7.5	25.6±12.2	13.0±4.2
HOMA-IR (x±SD)	2.5±.2.8	5.2 ±0.2	2.0±0.8	2.9±3.2	6.0±0.2	2.2±1.3

Table 4. The impairment of glucose and insulin levels during OGTT in patients with chronic hepatitis B and C, and those with and without steatosis.

Parameter	CHB			CHC		
	Total (n=100)	Steatosis (+), (n=44)	Steatosis (-), (n=56)	Total (n=100)	Steatosis (+), (n=45)	Steatosis (-), (n=55)
Impaired glucose tolerance (n/%)	30 / 30%	22 / 50%	8 / 14%	20 / 20%	18 / 40%	2/4%
Diabetes mellitus (n/%)	20/20%	18/41%	2/4%	30/30%	25/55%	3/5%
Insulin (UI/ml), (60 min - OGTT), (x±SD)	121±100.5	123±71.4	119±98.3	121±102.7	124±89.2	120±96.2
Insulin (UI/ml), (120 min- OGTT), (x±SD)	96±82.5	116±75.2	76±80.1	110±92.8	128±82.5	99±89.2

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